DISSERTATION ON

A CLINICAL STUDY ON CYSTOID MACULAR EDEMA

Submitted in partial fulfillment of requirements of

M.S.OPHTHALMOLOGY

BRANCH – III

REGIONAL INSTITUTE OF OPHTHALMOLOGY

MADRAS MEDICAL COLLEGE

CHENNAI – 600 003

THE TAMIL NADU DR.M.G.R.MEDICAL UNIVERSITY,

CHENNAI

MARCH 2014

CERTIFICATE

This is to certify that the dissertation titled, **"A CLINICAL STUDY ON CYSTOID MACULAR EDEMA"** is a bonafide record of the research work done by DR.DIVYA.P, post graduate in the Regional Institute of Ophthalmology & Government Ophthalmic Hospital, Madras Medical College and Research Institute,Chennai-03,submitted in partial fulfillment of the regulations laid down by the Tamil Nadu Dr. M.G.R. Medical University, Chennai for the award of M.S.Ophthalmology Branch III, under my guidance and supervision during the academic years 2011-2014.

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DECLARATION BY THE CANDIDATE

I hereby declare this dissertation entitled **"A CLINICAL STUDY ON CYSTOID MACULAR EDEMA"** is a bonafide and genuine research work carried out by me under the guidance of Prof.Dr.R.Ravikumar and Prof.Dr.B.Radhakrishnan.

DATE :

PLACE**:** **DR.DIVYA.P**

ACKNOWLEDGEMENT

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I am ever grateful to the almighty GOD for always showering HIS blessings on me.

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
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CERTIFICATE OF APPROVAL

To
Dr. Divya .P,
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Dear Dr. Divya .P,

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled **"A Clinical study on cystoid macular edema"** No.35102013

The following members of Ethics Committee were present in the meeting held on 08.10.2013 conducted at Madras Medical College, Chennai-3.

1.	Dr. G. Sivakumar, MS FICS FAIS	-- Chairperson
2.	Prof. Ramadevi, Director i/c, Instt. of Biochemistry, Chennai	-- Member
3.	Prof. P. Karkuzhali, MD Director of Pathology, MMC, Ch-3	-- Member
4.	Prof. Kalaiselvi, MD Prof. of Pharmacology, MMC, Ch-3	-- Member
5.	Thiru. S. Govindasamy, BABL	-- Lawyer
6.	Tmt. Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

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ABSTRACT

TITLE – A Clinical Study On Cystoid Macular Edema

AIM : To study the epidemiology of cystoid macular edema and analyse the effectiveness of intravitreal triamcinolone acetonide in treatment of refractory cystoid macular edema.

MATERIALS AND METHODS : This prospective, non randomized clinical study was conducted at Regional Institute of Ophthalmology, Chennai in Vitreo retina clinic. 40 eyes of 32 patients were analysed and followed up for a period of 6 months.

OBSERVATIONS AND RESULTS : The mean age of presentation was 58.33 ± 9.5 years with a male : female ratio of 1.9:1. Diabetes was found to be the leading cause. The reduction in mean macular thickness was significant in all three groups with diabetic macular edema(423.13±196.55µm) and pseudophakic macular edema (450.55±126.38µm) having a good reduction compared to retinal vein occlusion group. All patients had a significant 2 Snellen line visual improvement. The correlation between macular thickness and visual acuity was weak positive in post treatment. Increase in intraocular pressure was noted in 22.5% cases responding to medical therapy with 1 case needed a surgical intervention.

CONCLUSION : The fall in Mean macular thickness after IVTA was statistically significant in all three groups analysed.The visual acuity improvement also was statistically significant ($p<0.0001$) but correlation with macular thickness was weak positive. Intravitreal triamcinolone acetonide is a promising therapy in refractory cystoid macular edema in terms of safety and effectiveness.

KEYWORDS : Refractory cystoid macular edema, mean macular thickness, visual acuity, intraocular pressure.

CONTENTS

PART - I

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ABBREVIATIONS

CME	–	Cystoid macular edema
FFA	–	Fundus fluorescein angiography
OCT	–	Optical coherence tomography
AC	–	Anterior chamber
NSAIDs	–	Non steroidal anti inflammatory drugs
Nd-Yag	–	Neodymium Yttrium Argon Garnet
ILM	–	Internal limiting membrane
CNVM	–	Choroidal neovascular membrane
CSR	–	Central serous retinopathy
RPE	–	Retinal pigment epithelium
NPDR	–	Non proliferative diabetic retinopathy
FAZ	–	Foveal avascular zone
CRVO	–	Central retinal vein occlusion
BRVO	–	Branch retinal vein occlusion
ERM	–	Epiretinal membrane
DM	–	Diabetes mellitus
TNF	–	Tumour necrosis factor
CSME	–	Clinically significant macular edema
ACIOL	–	Anterior chamber intraocular lens
PCIOL	–	Posterior chamber intraocular lens

OPL – Outer plexiform layer

DME – Diabetic macular edema

NFL – Nerve fibre layer

PAM – Potential acuity meter

ERG – Electroretinogram

FERG – Foveal electroretinogram

ETDRS – Early treatment Diabetic Retinopathy study

FDA – Food and drug administration

RP – Retinitis pigmentosa

PPV – Parsplana vitrectomy

ARMD – Age related macular degeneration

VEGF – Vascular endothelial growth factor

PKP – Penetrating keratoplasty

IVTA – Intravitreal triamcinolone acetonide

SCORE – Standard vs Corticosteroid for retinal vein occlusion study

RD – Retinal detachment

PART - I

INTRODUCTION

Retinal edema is a common condition occuring due to circulatory disturbances and in inflammatory conditions. Macular edema is broadly defined as an abnormal thickening of macula with accumulation of excess fluid in the extracellular spaces of retina.

Cystoid macular edema is an accumulation of fluid in cyst like spaces within the macula in the outer plexiform layer. It is a common pathological response to a wide variety of ocular insults. It is thought that prostaglandin secretion and vascular endothelial damage causes fluid accumulation in the relatively loose intercellular adhesions of outer plexiform layer which permits the formation of cystoid spaces.

Macular edema due to various causes forms the leading cause of central vision loss in the world and therefore gained enormous importance.

Aphakic and Pseudophakic cystoid macular edema, commonly referred to as Irvine-Gass syndrome, has been recognised as a distinct entity since 1953 after its description by Irvine and Gass and by Norton in 1966. It is one of the most frequent and troublesome problem following cataract surgery. With recent improvements in sutures, instruments, techniques and antibiotic therapy, loss of central vision secondary to changes in macula following uneventful cataract extraction has received recognition as a major complication of cataract surgery.

REVIEW OF LITERATURE

1953 – Irvine described a syndrome of spontaneous rupture of the hyaloid face following uneventful cataract extraction. There was irritability of eye and decreased visual acuity secondary to vitreous opacities and macular degeneration.

1954 – Schepens noted attachment of the vitreous at the vitreous base, disc and macula.

1955 - Schepens reported macular clouding followed by a macular break which in turn lead to retinal detachment, due to vitreous shrinkage and traction.

1965 – Tolentino and Schepens presented a series of cases of edema of posterior retina after cataract extraction. In most of them they were able to demonstrate vitreous strands attaching to the macula and occasionally to optic disc. They attributed the change to vitreo-retinal traction.

1966 – Gass and Norton further described the condition and gave it the title “Cystoid Macular Edema”. They illustrated the characteristic clinical and FFA picture and described in detail the biomicroscopic appearance of the lesion.

1966 – Iliff gave the vitreous traction theory.

1968 – Gass and Norton did partial open sky vitrectomy under microscopic control using cellulose sponge and scissors.

1970 – Mechanized vitrector was used for limbal and parsplana vitrectomy.

1977 – Miyake first used NSAIDs like topical indomethacin in the treatment of CME following cataract surgery.

1983 – Katzen, Fleischman, Trokel used the Nd-Yag laser for vitreolysis.

1991 – Shahidi, Ogura determined that retinal thickness as measured by biomicroscopy and stereophotography correlates well with visual acuity.

1995 – Arend and Remby used fluorescein angiography generated with scanning laser ophthalmoscope for early recognition of cystoid formation in CME.

1995 – Hee and Puliafito used the optical coherence tomography for objectively monitoring retinal thickness in patients with CME.

ANATOMY OF MACULA

Macula is the optical, functional and organic focal point of the eye concerned with precise visual functions of acuity, form sense, colour, differentiation and stereopsis.

There is no anatomical landmark to define this zone on clinical examination or on morphological basis. It is approximately a circle with radius of 2.75mm centred at fovea (5.5mm in diameter). The yellow colour of macula is due to xanthophyll pigments in ganglion cells. The side walls of macula slope gently towards the fovea centralis.

Fovea centralis is the depression in the inner retinal surface in the centre of macula and is 1.5mm in diameter and 0.25mm in thickness.

Foveola is 0.35mm in diameter and 0.13 mm in thickness occupying centre of fovea. It is situated 4mm temporal and 0.8mm inferior to optic nerve head. Rod cone ratio is about 1:2 in this region.

A small depression in the centre of foveola is called umbo.

Parafoveal zone is an area measuring 0.5mm surrounding the fovea. Rod cone ratio is about 1:1.

Perifoveal zone is 1.5mm wide zone surrounding the parafoveal area.

BLOOD SUPPLY OF MACULA

Macular region is supplied by small twigs from superior and inferior branches of central retinal artery. In 20% of individuals, cilioretinal artery, a branch from the ciliary system of vessels supply the macula. Capillaries are arranged as three layered in the macula and they are reduced to single layer in the perifoveal area and in centre is the capillary free zone of 400-600µm in diameter.

BLOOD RETINAL BARRIER

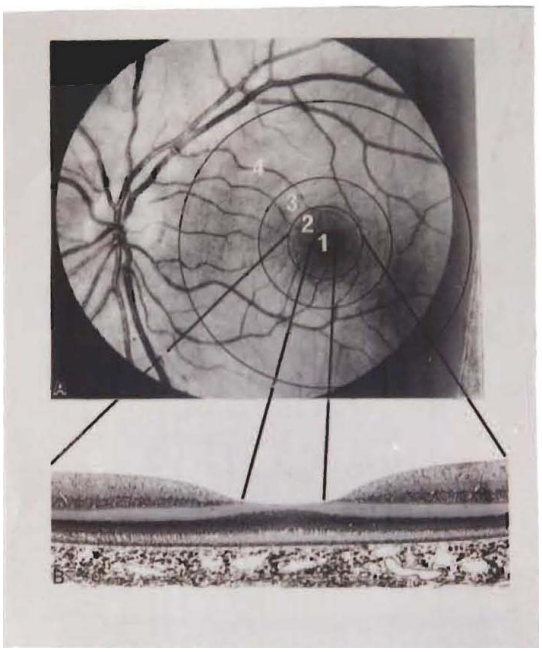
Outer Blood Retinal Barrier

This is formed by the tight junctions (Zonulae occludens and Zonulae adherens) of retinal pigment epithelial cells.

Inner Blood Retinal Barrier

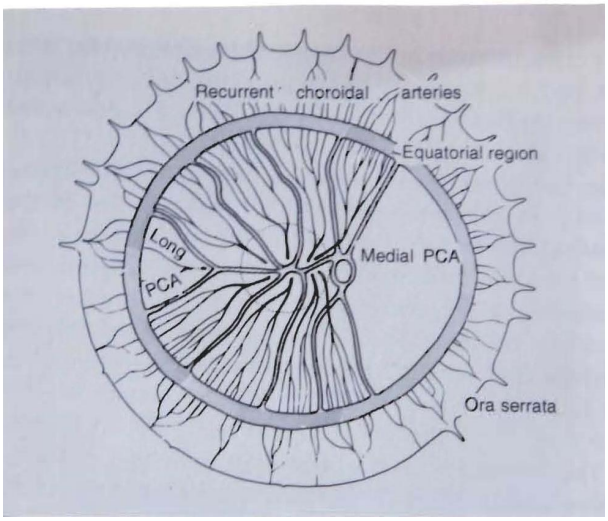
The endothelial cells of retinal capillaries are bound together about the lumen by intercellular junctions of zonulae occludens type and forms the inner blood retinal barrier.

ANATOMY OF FOVEA



(1) Foveola (2) Fovea centralis (3) Parafovea (4) Perifovea

BLOOD SUPPLY OF FOVEA



Dotted circle represents the macular region

MICROANATOMY OF MACULA

Retina at macula is made of three types of cells and their synapses arranged from without inwards in the following layers

- Retinal pigment epithelium
- Layer of rod and cones
- External limiting membrane
- Outer nuclear layer
- Outer plexiform layer
- Inner nuclear layer
- Inner plexiform layer
- Ganglion cell layer (multilayered in comparison to rest of retina)
- Nerve fibre layer
- Internal limiting membrane.

In Cystoid Macular Edema there is accumulation of fluid between outer plexiform and inner nuclear layer.

FOVEA CENTRALIS

This region is predominated by cones and are arranged obliquely forming the Henle’s layer.

FOVEOLA

This region of retina contains cones and their nuclei covered by thin internal limiting membrane. Remaining retinal layers (Inner nuclear layer, Inner plexiform layer, ganglion cell layer and nerve fibre layer) are absent in foveola.

HENLE'S FIBRE LAYER

The outer plexiform layer is made up of arborisation of axons of rods and cones with bipolar cell dendrites. It includes Muller's fibres and Horizontal cell processes. This layer has a reticular structure but as macula is approached it takes up a fibrous structure called Henle's layer. The fibres run vertically at first and then obliquely near macula and finally parallel to surface which is thickest at macula and absent at foveola. There is progressive disappearance of rods.(1)

ANATOMICAL PECULIARITIES OF MACULA CAUSING AN EXAGGERATED RESPONSE TO PATHOLOGICAL PROCESSES

The peculiar susceptibility of the macula to a number of different pathological processes, both local and general is called the “exaggerated response of macula” (2). Anatomical causes for this are:

Vascular supply – The arcade arrangement of capillaries which arise as terminal parts of an end artery system together with the central avascular zone make the foveolar region a watershed. Local impairment of metabolism whether from disturbances of perfusion and accumulation of metabolites or from the effects of capillary damage leads to extracellular fluid collection at a quicker rate than they can be absorbed. Also the capillaries at fovea are longer and vascular complexes are thinner than elsewhere hence they are more susceptible to noxious substances.

1. Tissue architecture – The processes of Muller’s cells run horizontally in outer plexiform layer hence retina loses its compact nature and this laxity enables large quantities of extracellular fluid to be accumulated in the macular region leading to characteristic cystoid edema.

2. Cellular constituents – The ganglion cells have high metabolic activity and their dysfunction leads to rapid accumulation of tissue metabolites. Most of these have a vasodilator effect and this along with the underlying hypoxia leads to edema.

3. Internal limiting membrane – The vitreous is an excellent diffusion medium and the ILM provides little additional interference to the progress of toxic substances diffusing across it. Inflammatory toxins arising from the iris, peripheral choroid and pars plana may traverse the vitreous and because of the thinness and adherence of ILM in foveal region, they may preferentially disturb the function of cells which are highly concentrated around foveal rim and also affect the macular capillary permeability.

4. Choroid and RPE – The macular choroid and RPE are also the preferential sites for degenerative changes which may be hereditary, toxic or arteriosclerotic in nature. There is a predisposition for choroidal vascular disease with decompensation and hemorrhage in the central area which is thought to be because, RPE in fovea is very active metabolically and this hyperactivity along with special hemodynamic effects of narrow choroidal capillaries in this region may lead to increased susceptibility.

EVALUATION OF MACULAR DISEASES

SLIT LAMP BIOMICROSCOPY

It utilises high power convex lenses to obtain wide field of view of the fundus which is vertically inverted and laterally reversed. It provides high magnification with stereopsis to detect macular disease.

AMSLER GRID TEST

It evaluates central 200 of visual field on fixation and hence useful in screening and monitoring the macular disease. There are 7 charts. Chart 1 is most commonly used. This chart consists of white grid on black background with 400 small, 5mm squares, each square subtends an angle of 10 when viewed at 33cm. Each eye is checked individually, with the chart held at 33cm with prior correction for presbyopia. Patients are asked to maintain fixation on the central dot and comment on four corners, any missing areas on chart and wavy lines.

FUNDUS FLUORESCEIN ANGIOGRAPHY

Fluorescence is the property of certain molecules to absorb light of shorter wavelength and emit light of longer wavelength. This is the

principle used in fundus fluorescein angiography and is valuable in evaluation of macular diseases.

Sodium fluorescein is a water soluble orange dye, 3ml of 25% fluorescein is injected intravenously through antecubital vein, 85% is bound to plasma proteins and remains intravascular. Passage of dye through retinal and choroidal circulations is studied through photographic surveillance.

- Phases in FFA – Choroidal phase, Arterial Phase, Arteriovenous phase, Venous phase, Recirculation phase.
- Causes of Hyperfluorescence – Autofluorescence, Pseudofluorescence, Window defect, Pooling, Leakage, Staining.
- Causes of Hypofluorescence – Masking of Retinal fluorescence, Masking of Choroidal fluorescence, Filling defects.

OPTICAL COHERENCE TOMOGRAPHY

OCT is a non invasive, non contact imaging system that provides high resolution cross sectional images of retina, optic nerve head and the vitreous.

Principle – OCT is based on imaging of reflected light (near infrared light), analogous to B scan. The difference is that OCT uses low coherence interferometry and measures optical rather than acoustic or radiowave reflectivity.

OCT is used to differentiate lamellar and full thickness macular hole, to determine treatment options in CNVM, monitoring the course of CSR, retinal thickness map, to identify type of macular edema and to monitor its course and so on.

- High Reflectivity – Nerve fibre layer, RPE, Choriocapillaries, Pigment accumulation, Naevus, Neovascularisation, RPE hypertrophy.

- Medium reflectivity – Plexiform layer.

Low Reflectivity – Nuclear layer, Photoreceptors, Retinal edema, Cystoid edema, Cavity, Cyst, Pigment epithelial detachment, Serous retinal detachment.

The macular edema patterns seen on OCT are as follow:

1. Sponge like Retina

It is mostly confined to outer retinal layers ue to backscattering from intra retinal fluid.

2. Cystoid macular edema

Cystoid spaces confined to outer retina mostly. In long standing cases they fuse to form large cyst.

3. Serous retinal detachment

Hypo reflective space under fovea. It may disappear following laser.

4. Tractional retinal detachment

Foveo vitreal traction causes detachment of fovea. Its an indication fors Pars Plana Vitrectomy to release traction. Laser will worsen macular edema in these cases.

5. Taut Posterior Hyaloid Membrane

Cystoid spaces confined to outer retina mostly. In long standing cases they fuse to form large cyst.

CYSTOID MACULAR EDEMA

The extracellular space of the retina normally constitutes a small proportion of its total volume. Active transport of electrolytes and larger molecules from retina across the retinal pigment epithelium to the blood maintains this space. Disruption of either inner or outer retinal barrier leads to leakage of plasma proteins and water which leads to expansion of extracellular space of retina. This is often accompanied by accumulation of fluid in the outer plexiform and inner nuclear layer of retina. Retinal edema localized to macula is called macular edema leading to diffuse thickening of posterior pole. Accumulation of fluid in cystic spaces leads to cystoid macular edema.

CAUSES OF CYSTOID MACULAR EDEMA

Cause of cystoid degeneration of macula as described by Duke Elder are [3]

1. Senile degeneration.
2. Vascular disorders - Arteriosclerosis, CRVO, CRAO, Retinal periphlebitis, Hypertensive retinopathy, Diabetic retinopathy.

3. Inflammatory conditions - chorioretinitis, iridocyclitis.

4. Degenerative conditions of macula - Retinal dystrophies, Retinitis pigmentosa.

5 Trauma - usually in contusions or associated with retention of foreign body, radiation injury like eclipse blindness.

6. Glaucoma.

7. Hereditary macular dystrophy.

Other conditions as mentioned by Stephen J. Ryan are[4]

8. Drugs - Epinephrine maculopathy, Nicotinic acid maculopathy.

9. Post surgical - After any type of cataract surgery, vitrectomy, glaucoma procedures, penetrating keratoplasty.

10. Tumours - choroidal hemangioma, choroidal melanoma.

11. Retinal detachment.

12. Tractional maculopathies – Epiretinal membrane, Vitreomacular traction syndrome.

13. Optic nerve head abnormalities – Optic disc pit, coloboma, diabetic papillopathy.

CME IN RETINAL VASCULAR DISEASES

- **Diabetic Cystoid Macular Edema**

It is the most common cause of visual impairment in patients with NPDR. This is best detected by slitlamp biomicroscopy with +90 D, +78 D and Fundus contact lens.

Incidence of macular edema increases with type of diabetes, duration of diabetes, age of onset, use of insulin, uncontrolled diabetes, associated risk factors like hypertension, hyperlipidemia, anemia, nephropathy. It is more common in type 2 diabetes.

Pathophysiology

Hyperglycemia is the main inciting factor which causes disruption of retinal vasculature that breaks blood retinal barrier and leakage from microaneurysms and capillaries. Focal retinal hypoxia causes an increase in hydrostatic pressure that in turn increases luminal hydrostatic pressure. This causes dilatation of capillaries with disruption of tight junctions between endothelial cells and favouring fluid egress and macular edema.

Clinical features

1. Thickening of macula
2. Blurring of underlying choroidal vascular pattern
3. Loss of foveolar reflex
4. Cystoid spaces
5. Lipid exudation from leaking microaneurysms forming circinate maculopathy.

Classification of types of edema

1. Focal Edema – Areas of focal leakage from microaneurysms forming partial or complete ring of hard exudates delineated from adjacent healthy retina.

2. Diffuse Edema – Areas of leakage from microaneurysms and dilated capillary segments throughout posterior retina causes diffuse edema. It differs from focal edema by

    a) Diffuse edema is not associated with hard exudates.
    b) It develops cystoid spaces more commonly and better seen in late phases of FFA and on OCT as hyper reflective spaces with hyper reflective septa.
    c) It is bilaterally symmetrical.

d) It may disappear spontaneously even without laser only to reappear spontaneously.

e) Systemic features may be associated with exacerbations and amelioration of diabetic macular edema.

3. Ischemic Edema – It is associated with enlargement of FAZ, irregularties of FAZ, capillary budding into FAZ, widening of intercapillary spaces and capillary dropout in perifoveal area.

Clinically Significant Macular Edema (CSME)

1. Thickening of retina within 500µm from centre of macula.
2. Hard exudates with retinal thickening seen within 500µm from centre of macula.
3. A zone of retinal thickening about 1 disc diameter in size, a portion of which is seen within 1 disc diameter from centre of macula.

FFA

Focal edema shows areas of leakage mainly from microaneurysms in late phases. Diffuse edema shows dilated capillary network with areas of capillary nonperfusion with extravasations of dye in late phases. If leakage occurs in flower petal pattern, cystoid macular edema is present.

DIABETIC MACULAR EDEMA

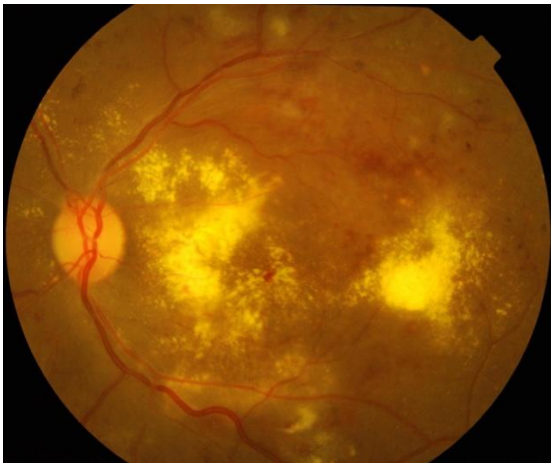


Figure -1 Colour Fundus

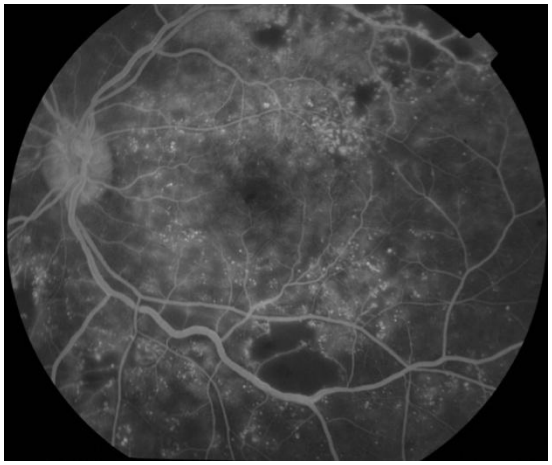


Figure - 2 FFA early Phase

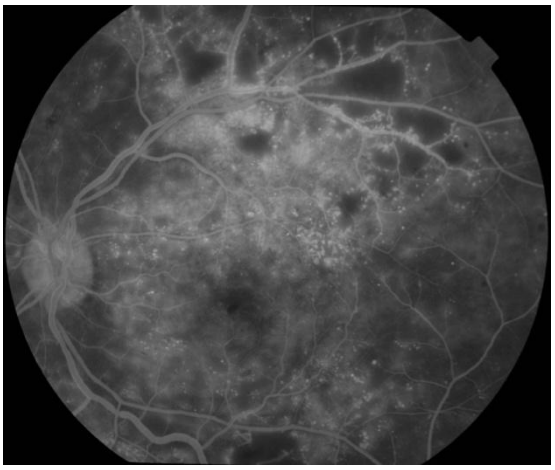


Figure - 3 FFA Mid Phase

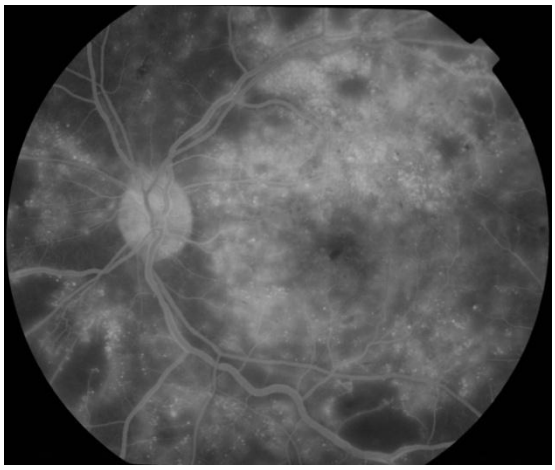


Figure - 4 FFA Late Phase

- **Retinal Vein Occlusion Induced Cystoid Macular Edema**

In CRVO and BRVO, macular edema tends to be chronic, difficult to treat and visually disabling. Visual loss is exacerbated by macular haemorrhages, macular ischemia, secondary RPE changes like ERM.

Pathophysiology

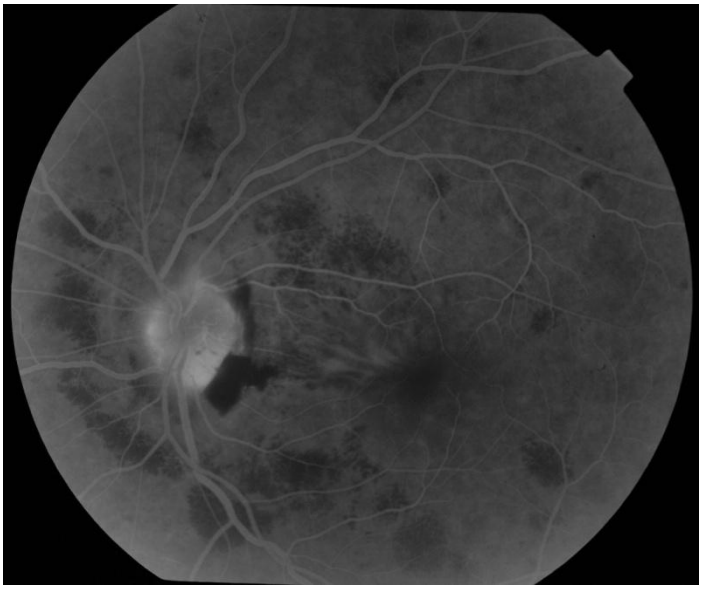
- Elevation in intravascular pressure in the retinal veins distal to occlusion site causes increase in transmural hydrostatic pressure in retinal capillaries leading to greater transudation of fluid into extracellular spaces.

- Disruption of microscopic intraretinal connections due to cytokines mediated by hypoxic retina greatly facilitates extravasation of fluids as well as large protein molecule[(5)].

- Development of fluid blood levels in central cystoid spaces is characteristic of obstructive retinopathy.

CRVO WITH CYSTOID MACULAR EDEMA

FFA PICTURE



POST OPERATIVE CYSTOID MACULAR EDEMA

It is the most common cause of vision loss after cataract surgery. A higher incidence is seen when surgery is complicated by vitreous loss, vitreous adhesions to cataract wound, iris damage or retained lens material.

The risk of developing CME is higher in patients with associated factors like DM and Uveitis (vasoactive stimuli).

Pathophysiology

- **Vitreous Traction Theory**

Constant constriction and dilatation of pupil created pulling effect on the anterior vitreous strands which was transmitted to the vitreous base and to macula by presumed vitreous connections between posterior hyaloid and surface of macula- VITREOUS TUG SYNDROME.

- **Inflammation Theory**

CME following cataract extraction (Irvine-Gass) syndrome can be seen in approximately 20% of uncomplicated cases.[6]

Eyes with CME nearly always demonstrate signs of intraocular inflammation and responds to steroid therapy. Aqueous humour contains biochemically active principles called Aqueous Biotoxic Complex factors which manifest biotoxic effects when it leaves its natural reservoir. These diffuse posteriorly through collapsed liquefied vitreous gel. The liquefied vitreous anterior to retina assumes chemical and osmotic properties that are not normally present resulting in outpouring of fluid from perimacular capillaries.

Since eye does not contain enzyme 15-Pg dehydrogenase to deactivate prostaglandins, their removal is dependent on active transport pump called Bito's[23] pump located in the ciliary epithelium which is inoperable for atleast 3weeks post trauma.

Inflammatory state persists for longer periods when vitreous is adherent to cataract wound causing pupillary distortion.

- **Anoxic Theory**

An association between CME and systemic conditions like hypertension, diabetes mellitus, arteriosclerotic disease is seen in which anoxia could be a predisposing factor.

CME In ACIOL

Chronic uveal irritation may either stimulate production of intra ocular inflammatory substances or may retard the absorption or removal of these substances by non pigmented epithelium of ciliary body. An ACIOL can press against anterior surface of iris or apply constant pressure over ciliary body which could trigger anterior uveal inflammation.

CME In PCIOL

1. No pupillary distortion and intact posterior capsule
    a. Sulcus fixated IOL – chronic irritation of uveal tissue because of direct contact can lead to CME
    b. In the bag IOL – Incidence of CME is low.

2. Pupillary distortion – Distortion by pupillary capture or by synechiae between remnants of anterior capsule and posterior surface of iris can lead to persistent uveal irritation leading to CME. The degree of irritation is not as great as produced by pupil distorted by wick of vitreous adherent to corneoscleral wound.

CME In Phacoemulsification

There could be a greater incidence during learning curve because of increased intraocular manoeuvring and greater risk of complications.

CME In Posterior Yag Capsulotomy

1. Primary Surgical Posterior Capsulotomy

There is a higher incidence of CME because posterior capsule acts as a barrier to posterior diffusion of inflammatory mediators and to anterior movement of vitreous.

2. Secondary Nd-Yag Capsulotomy

- Broken capsule no longer acts as a barrier for posterior diffusion of inflammatory mediators.
- Inadvertent rupture of anterior hyaloid face.
- Post laser intraocular inflammation.

CME IN UVEITIS

Pathophysiology

Disruption of blood retinal barrier secondary to inflammatory mediators like Cytokines, Interferon-ɣ, Interleukin-2 and 10, TNF-α.

THEORIES CONCERNING ORIGIN OF CYSTS OF CME

- **Intracellular Theory**

Yanoff et al. proposed that cysts develop from degenerating Muller's cells. Initially these cells demonstrate edema which gradually increases until cytoplasm of cells begin to develop vacuoles. These edematous cells gradually expand until cell walls break and adjoining cells form larger cavities leading to cysts in CME. A breakdown in blood retinal barrier or anoxia is the prime cause for edema.

- **Extracellular Theory**

Gass, Anderson and Davis proposed that cysts arise from expansion of extracellular spaces of retina by serous exudation within the outer plexiform layer and inner nuclear layer. This involves leakage of serous exudates from perifoveal intraretinal capillaries and sometimes from disc capillaries. These exudates form small puddles in OPL of Henle which acts like a sponge because of peculiar nature of macula.

This theory is supported by highly reversible function of CME eye which argues against cellular death and disruption and, visible lack of occluded capillaries in macula which argues against presence of anoxia.

CLINICAL FEATURES OF CYSTOID MACULAR EDEMA

SYMPTOMS

It is usually asymptomatic. If severe, defective vision, metamorphosia, scotomas can occur.

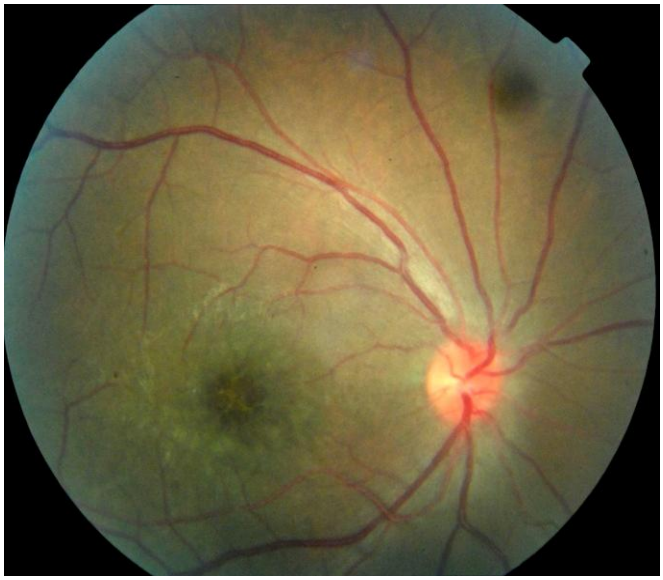
SIGNS

Fundus

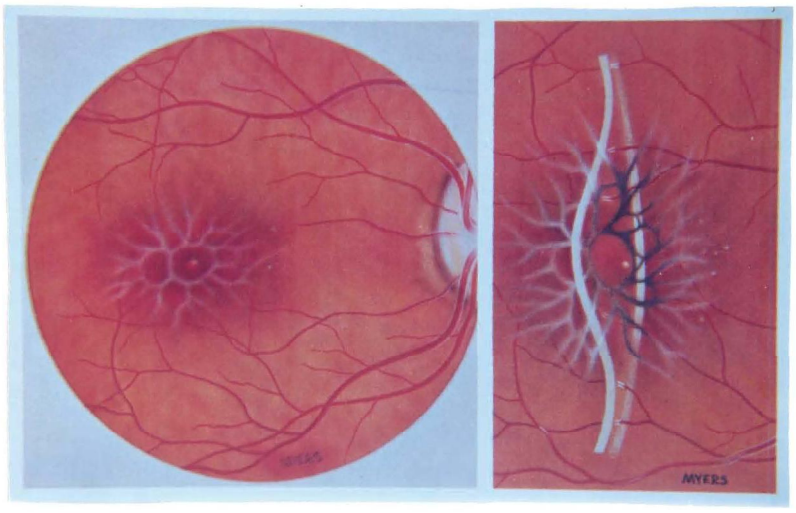
- Characteristic honey comb like lesion showing one or more cystoid spaces centrally with many small oval spaces around them.
- Sometimes only loss of foveal reflex is seen.
- Cystoid spaces are best seen with red free filter which makes inner walls visible.
- Retina may be markedly thickened and lesion as large as 1.5-2 disc diameters.
- Some cases are associated with disc edema.

Anterior segment- Usually shows signs of inflammation. The anterior hyaloid face is broken or intact and vitreous shows cells, vitreous opacities and posterior vitreous detachment.

COLOUR FUNDUS PHOTOGRAPH OF CYSTOID MACULAR EDEMA



DRAWING OF FUNDUS AND BIOMICROSCOPIC APPEARANCE OF CME



(as originally drawn by Gass and Norton in 1966)

CLINICAL EVALUATION OF CYSTOID MACULAR EDEMA

1. VISUAL ACUITY

Best corrected visual acuity and with pin hole should be assessed. Loss of vision depends on the involvement of macula. Severity of vision loss correlates well with amount of macular edema.

2. PERIMETRY

Field charting by perimetry may reveal scotoma corresponding to areas of involvement in fundus.

3. COLOUR VISION

The most common defect is blue . In diabetes the sensitivity of blue cones is depressed. These are best detected by Farnsworth munsell 100 hue test.

4. DIRECT OPHTHALMOSCOPY

Monochromatic light is better for detecting subtle macular changes, hence red free light is used. But lack of stereoscopic view is a disadvantage.

5. SLIT LAMP BIOMICROSCOPY WITH 90D, 78D, HRUBY LENS, GOLDMANN THREE MIRROR CONTACT LENS

The optical section of convex anterior walls of cysts can be seen overlying empty vesicles tightly packed together with their interfaces presenting a spidery pattern.

With slit beam, it is possible to see a network of interlacing fine refractile lines by retroillumination.

Advantages of using stereopsis and slit lamp optics.

6. INDIRECT OPHTHALMOSCOPY

This provides an entire view of retina allows examiner to have an understanding of the cause in various pathological features of retina.

It gives less magnification.

7. RETINAL PHOTOGRAPHY

Photographs are taken with fundus camera and selected films and colour filters. Red free light is used for detecting subtle changes in ILM and NFL.

8. STEREOPHOTOGRAPHY

Two photographs are taken along parallel axes on either side of dilated pupil producing stereoscopic pair. The separation of images can be adjusted to reproduce the normal depth relationships and to allow depth measurements.

9. MADDOX ROD TEST

The patient is asked to look at distant light through a Maddox rod. If the red line is continuous and unbroken, macular function is good.

10. AMSLER GRID TEST

Central distortion of the grids or a relative central scotoma may be seen in CME.

11. ENTOPTIC IMAGERY

The globe is steadily and firmly massaged through the closed lower lids, with bare lighted bulb of a torch. The entire vascular tree of the retina is seen on an orange background. Any blanks or scotoma in the central area implies macular involvement.

12. POTENTIAL ACUITY METER

It is for differentiating between visual loss from anterior segment disease and macular disease. The PAM attaches easily to a standard slit lamp and projects a Snellen's visual acuity chart into eye using a 1.5mm diameter pin hole aperture. The patient is tested at different points on the cornea in an attempt to project through the clearer areas in the lens.

13. MACULAR PHOTOSTRESS TEST OR AFTER IMAGE SCOTOMETRY

The patient looks at a flash light held 2cm from the eye for 10 seconds. The time it takes for visual recovery to one line less than the visual acuity determined prior to this test is measured. The normal recovery time is 55seconds. Longer recovery time, upto 90-180 seconds implies macular dysfunction even though the area may appear anatomically normal. The rapidity of recovery relates to the rate of visual purple regeneration and rapidity of vitamin A transport from RPE to photoreceptors. Difference between two eyes is also significant.

14. CLINICAL INTERFEROMETERS

In cases of opaque media, beams of coherent light from two point sources are directed through the clearest area of the lens into retina. Interference fringes on the retina are formed wherever the two beams overlap and by varying the width of the inter fringe pattern, the visual acuity can be determined.

15. ELECTROPHYSIOLOGICAL ASSESSMENT

Foveal ERG is a test of the temporal responsiveness of the central 100 of the retina and requires integrity of the outer retinal layers, especially Muller's cells. FERG is usually abnormal in 35% of eyes with CME. Pattern ERG reflects the inner retinal layer function. It is usually abnormal in 53% of eye with CME. It is the test of the temporal responsiveness of central 100 of the retina.

16. VISUAL EVOKED POTENTIAL

In macular disease with fluid accumulation, the VEP shows amplitude reduction depending on the decreased visual acuity with no change in latency.

IMAGING MODALITIES IN CYSTOID MACULAR EDEMA

➢ FUNDUS FLUORESCEIN ANGIOGRAPHY

FFA is mandatory for following purposes:

- Confirm and document macular changes
- Deciding the management
- Follow up.

It allows examination of structures in the macular region which are beyond the reach of direct ophthalmoscopy and also helps to study the hemodynamic changes that occur in the retina and localized abnormalities of flow and perfusion that are the background to many pathological disturbances.

In CME, within 1-2 minutes of injection, in the arteriovenous phase, early leakage of the dye in the parafoveal area is seen. In some instances, focal points of leakage with confluence of leaking areas will be noted. A characteristic flower petal appearance is evident in late arteriovenous phase in the parafoveal region. Fovea itself appears dark and does not always show leakage. The late phase shows marked edema with persistent pooling of dye in cystoid spaces.

The dark septae in the macular area which compartmentalize the pattern are because of the Muller's fibres. The spaces appear to intercommunicate. Usually there is considerable leakage of dye into vitreous and aqueous anteriorly. In some patients with disc edema, there may be leakage of dye into optic nerve and peripapillary retina.

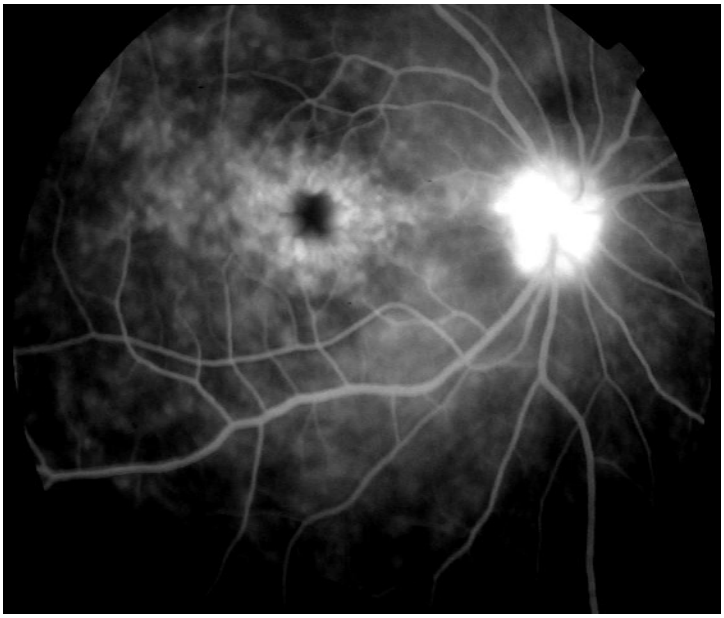
- **OPTICAL COHERENCE TOMOGRAPHY**

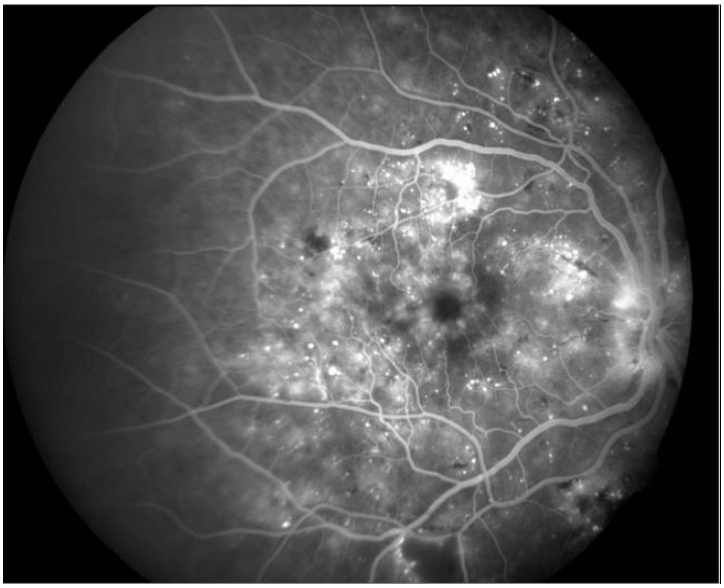
This investigative modality can also be used for diagnosis and follow up. It has added advantage of being non-invasive.

In addition parameters like macular thickness can be quantified on subsequent visits.

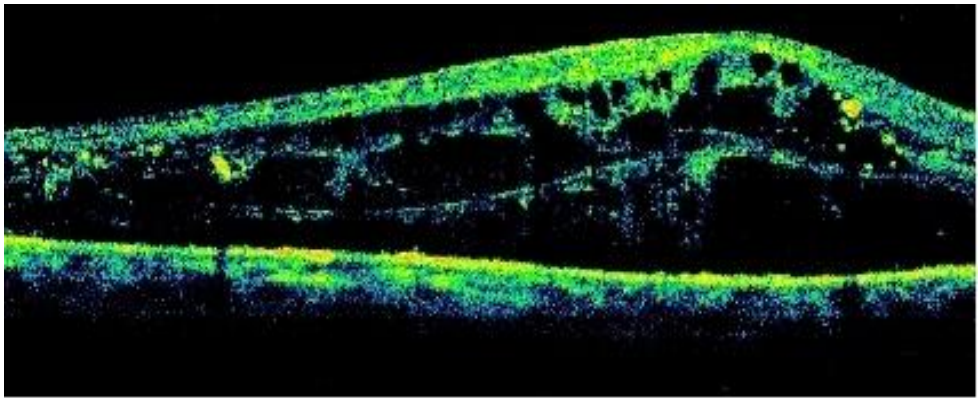
Cystoid spaces confined to outer retina mostly. In long standing cases they fuse to form large cyst.

FFA PICTURE SHOWING CHARACTERISTIC FLOWER PETAL LEAKAGE PATTERN

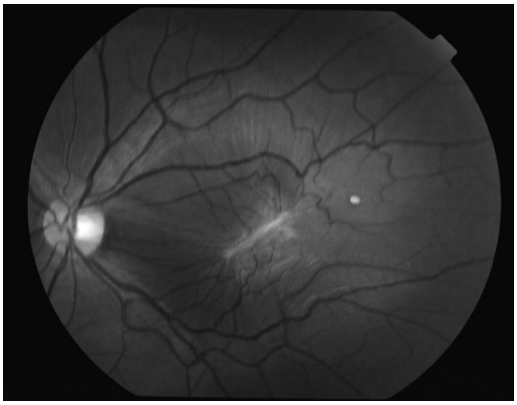




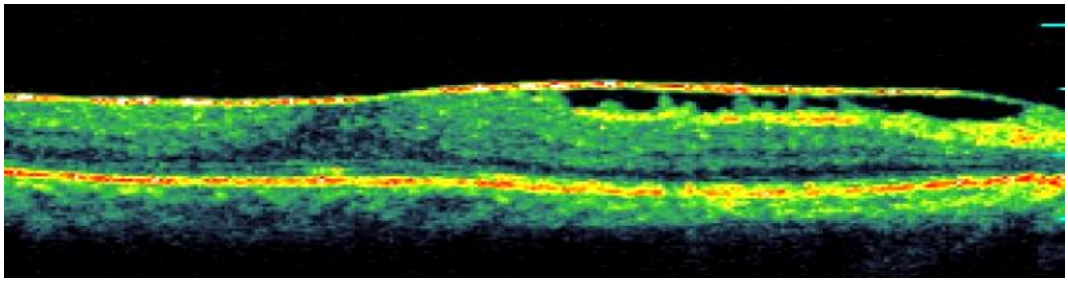
OCT PICTURE SHOWING CYSTOID SPACES



EPIRETINAL MEMBRANE



OCT PICTURE SHOWING EPIRETINAL MEMBRANE



TREATMENT MODALITIES FOR MACULAR EDEMA

1. LASER PHOTOCOAGULATION

Macular edema secondary to vascular causes like diabetic retinopathy and retinal vein occlusions respond well to focal and grid laser photocoagulation. Focal laser is used to close microaneurysms and grid laser stimulates RPE pump to clear the edema.

The Early Treatment for Diabetic Retinopathy Study (ETDRS) established guidelines for laser treatment in diabetic macular edema[7]. Laser treatment is indicated for clinically significant macular edema as per definition stated before. Moderate visual loss was reduced to 50% in patients who received laser therapy in ETDRS.

Grid laser has proven benefit in patients with BRVO but not in CRVO. In Branch Vein Occlusion Study, 65% of grid laser treated eyes gained atleast 2 lines of vision, compared with 37% of untreated eyes[8]. In Central Vein Occlusion Study, grid laser did not have any significant effect on vision, although there was a trend towards better vision in patients aged <60 years who underwent laser treatment.

2. MEDICAL MANAGEMENT

➢ TOPICAL THERAPY

Several studies have documented the utility of topical NSAIDs for both the prevention and treatment of macular edema after cataract surgery[9]. A double masked, randomized, placebo controlled trial to evaluate the effect of Ketorolac 0.5% ophthalmic solution on chronic pseudophakic and aphakic CME determined that this drug is beneficial for the primary outcome measure (Snellen's acuity)[10]. The efficacy of topical Flurbiprofen 0.03% and Indomethacin 1% in preventing pseudophakic CME was examined in a randomized, double masked study that revealed a reduced incidence of clinical and angiographic CME in the early postoperative period. Recently, two new topical NSAIDs, Bromfenac 0.09% and Nepafenac 0.1% have been FDA approved for cataract surgery inflammation and pain. There have been reports, particularly for Nepafenac, of their potential for preventing pseudophakic CME.[11] Nepafenac is a prodrug that is converted after corneal penetration to Amfenac, a potent NSAID. In one animal model, Nepafenac was shown to inhibit prostaglandin in the vitreous humour to a much greater extent than other traditional NSAIDs. Whether this efficacy

will translate into improved prevention or treatment of pseudophakic CME is currently under investigation.

Corticosteroids drops alone or in combination with NSAID drops, have been studied for the treatment of pseudophakic CME. Treatment with topical NSAIDs appears to be more effective than topical steroids alone. However, combination therapy with topical NSAIDs and Prednisolone acetate was superior to either one alone in treating CME. Consensus for topical NSAIDs use has not been established formally, however, the standard of care for many cataract surgeons is to use both NSAIDs and topical steroids for atleast 1 to 2 days preoperatively and for several weeks postoperatively. In higher risk patients, such as those with pre-existing ocular inflammation or diabetes, extended preoperative and postoperative use is typically employed. Patients must be monitored for side effects of both NSAIDs (corneal toxicity) and corticosteroid use (increased intraocular pressure).

- **SYSTEMIC THERAPY**

  - Systemic NSAIDs have been examined as a treatment of uveitic CME. A recent study of oral Naproxen or Rofecoxib revealed that these medications had no effect on CME. However, these

patients also had active, intraocular inflammation. NSAIDs may have a role in the prevention of recurrence of CME after inflammation is controlled, although this scenario is still under investigation[12]. The potential for NSAIDs to cause gastrointestinal ulceration or liver toxicity must be addressed with patients before initiating this therapy.

- Carbonic anhydrase inhibitors reduce macular edema that can occur in association with retinitis pigmentosa (RP). A randomized crossover study demonstrated that improvement in visual acuity in >80% of all RP patients who received Acetazolamide[13]. The usual starting dose is 500mg/day. Sometimes these are also used to treat uveitis associated CME, although potential benefits have not been established. There is also a conflicting evidence for CAI use, as in one study group there was a significant improvement in visual acuity in treated group while another failed to show an improvement despite reduction in macular edema evident on FFA[14]. The usefulness in pseudophakic CME is even less robust.

- Systemic corticosteroids have a long history of use in treatment of uveitic CME. In severe cases, intravenous steroids are

recommended during induction therapy. Treatment is initiated with high dose of 1mg/kg body weight, followed by a slow taper over several weeks to months. Tapering the steroids too rapidly is associated with higher recurrence. The short term side effects of steroids are mood alterations, difficulty sleeping, increased appetite, potential for worsening of a diabetic state. There are a few reports of successful use of systemic steroids in the treatment of recalcitrant cases of pseudophakic CME.

- Steroid sparing immunomodulators have also been useful in uveitic CME but its utility in macular edema is less clear.

PERIOCULAR CORTICOSTEROIDS

Corticosteroids are used in treatment of macular edema as they influence by multiple pathways, the factors responsible for breakdown of blood retinal barrier and edema. They inhibit VEGF and other cytokines and growth factors that regulate endothelial tight junctions. They also reduce the synthesis of prostaglandins and leukotrienes, potent inflammatory mediators. Periocular steroids may be given as peribulbar or subtenon’s space with equivalent benefit. Both these methods give a more sustained treatment than topical steroid drops alone. Peribulbar

injections give a short term benefit in some cases of macular edema induced by Diabetes, BRVO, CRVO, Pseudophakia. Periocular injections are of particular benefit in cases of uveitis that are not responsive to topical therapy. They decrease both inflammation and retinal thickening produced by macular edema.

- **INTRAVITREAL STEROIDS**

Corticosteroids by their anti inflammatory effect will contribute to reduction in edema. Increased diffusion by modulation of calcium channels also could account for efficacy of corticosteroids.[15]

In last few years, intravitreal triamcinolone (IVTA) has gained widespread use as a treatment in all forms of macular edema. IVTA reduces retinal thickening on OCT and improves vision in a substantial number of patients. Patients with cystoid component respond better. The duration of effect varies and macular edema recurrence and visual decline are observed 4 to 6 months after injection. Repeated therapy is often limited by side effects. Intraocular pressure elevation occurs in about one third of patients, which can (rarely) require glaucoma surgery. Acceleration of cataract formation, endophthalmitis are other

complications associated with the procedure which should be considered and discussed with the patient as a part of informed consent.

IVTA has also been used in macular edema associated with vein occlusion. A recently published 1 year study revealed a short term visual benefit in patients with CRVO associated macular edema who were treated for macular edema with IVTA, although their vision generally returned to pretreatment levels at 1 year despite repeated injections[16]. It has also been observed that rate of intraocular pressure rise and need for glaucoma surgery appears to be higher in this subset of patients than in those with diabetic macular edema. The SCORE (Standard Care Vs Corticosteroid for Retinal Vein Occlusion) Study, a National Eye Institute – sponsored randomized clinical trial of intravitreal steroid for BRVO and CRVO associated Macular edema clearly mentions the benefit of IVTA as compared to standard therapy in CRVO. In cases of macular edema due to BRVO, IVTA and Grid laser shows a comparable response, however, IVTA can be used for macular edema not responding to grid laser therapy.

Finally IVTA has been used in uveitic CME. A retrospective review of 16 patients with chronic, refractory uveitic CME who received atleast 1 injection of IVTA had results that mirrored those seen when this

medication was used as a treatment for macular edema caused by other diseases[17]. At a mean follow up of 34 weeks, there was a sustained improvement in visual acuity in 55% patients, although there was a relapse or persistence of CME in half of all patients receiving this treatment. One of the 20 eyes required glaucoma implant surgery for increased intraocular pressure.

➢ INTRAVITREAL DRUG DELIVERY SYSTEMS

Recently multiple alternative steroid delivery devices has arrived for treatment of macular edema. There are currently four corticosteroid-based intravitreal implants under development.

These include:

- Dexamethasone biodegradable implant (Posurdex®)
- Helical triamcinolone acetonide implant (I-vation™)
- Fluocinolone acetonide implant (Retisert®)
- Fluocinolone acetonide – based implant that is injectable (Medidur™)

OZURDEX is an intravitreal implant containing 0.7 mg (700 mcg) dexamethasone in the NOVADUR solid polymer drug delivery system.Iteffective in reducing macular edema for a period of 3 months.

OZURDEX – INTRAVITREAL DEXAMETHASONE IMPLANT

OZURDEX APPLICATOR

INTRAVITREAL ANTI VEGF COMPOUNDS

Anti VEGF agents work to restore the normal permeability of the blood retinal barrier. Pegaptanib sodium, an anti VEGF pegylated aptamer, has been studied in a phase II randomized, double blind, controlled trial of DME in 172 subjects.[18] Patients received atleast 3 injections at 6 week intervals and were followed for 36 weeks. The patients assigned to pegaptanib were more likely to gain atleast 10 letters (34% vs 10%, p=0.003) were more likely to show a reduction in central macular thickness (42% vs 16%, p=0.02) and at follow up examinations were deemed less likely to need additional photocoagulation therapy (25% vs 48%, p=0.04).

Ranibizumab (LucentisTM), another intravitreal anti VEGF agent that has been FDA approved for treatment of wet age related macular degeneration, was studied in a small series of 10 patients with DME and found to significantly reduce foveal thickness and improve vision[19]. Larger randomized trials are necessary to assess the significance of this preliminary finding.

Bevacizumab (AvastinTM) is a recombinant, humanized, monoclonal antibody directed against VEGF. Avastin has received FDA

approval as an intravenous drug for treatment of metastatic colon cancer. An intravitreal formulation was first used off label for the treatment of ARMD. In cases of diffuse DME that failed other treatments, intravitreal injection of Bevacizumab was associated with improved vision and decreased retinal thickness 12 weeks after the first injection[20]. Most of the patients received >1 bevacizumab injection during follow up. A recent study of intravitreal bevacizumab treatment for macular edema in patients with CRVO revealed a significant decrease in mean central thickness (887 to 372µm, $p< 0.001$), and improved visual acuity (defined as halving the visual angle) in 14 of 16 eyes[21]. Patients had received an average of 2.8 injections and were followed for a mean of 3 months. No adverse outcomes occurred. These encouraging short term results need to be validated in prospective studies. Bevacizumab has been tried in patients with macular edema secondary to uveitis. In one case series, in which patients were followed for atleast 2 months after a single intravitreal njection, about 70% of treated patients had a decrease in foveal thickness but only 40% of patients had improved visual acuity by >2 lines.[22] Thus for patients with difficult to control macular edema, bevacizumab may be a therapeutic option with reasonably good outcomes.

➢ Nd-Yag LASER VITREOLYSIS

Elevated vitreous strands are transacted using Nd-Yag laser. Bisecting vitreous membranes that are adherent to the anterior surface of iris may be difficult without producing small haemorrhages which diffuse into aqueous and make accurate focussing impossible. Therefore laser treatment is primarily used in those cases in which vitreous strands bridge the margin of pupil to undersurface of cataract wound without adhering to anterior surface of iris.

➢ SURGICAL THERAPY

S.NO	SITUATIONS	OPTIONS
1.	Intracameral lens within the pupil iris suspended	Remove/exchange for flexible ACIOL or SFIOL
2.	ACIOL with / without distorted pupil with vitreous in AC	Vitrectomy (for restoration of distorted pupil) with secondary IOL
3.	PCIOL with pupillary capture	Free the capture
4.	PCIOL with moderate papillary distortion from vitreous strands	Anterior vitrectomy for restoring pupil and consider leaving IOL
5.	PCIOL sulcus fixated with normal pupil	Consider removing IOL with / without 2^0IOL
6.	PCIOL in the bag with normal pupil	Rule out other causes of CME and PPV if there is a evidence of traction on macula.

CME DUE TO OTHER CAUSES

- **AGE RELATED MACULAR DEGENERATION**

CME occurs if serous detachment present for 3-6 months or if subretinal neovascularisation has progressed to cover subfoveal area.

Causes are anoxia and RPE destruction.

Treatment by any therapy has a poor prognosis.

- **CHOROIDAL TUMOURS**

Malignant melanoma, capillary hemangioma, naevi can cause CME due to prevention of nutrients and oxygen from reaching the retina.

Treatment is to treat the cause.

- **CHRONIC UVEITIS**

CME is due to breakdown of blood retinal barrier.

Treatment is to treat uveitis.

- **RETINITIS PIGMENTOSA**

RPE and perifoveal capillaries are more permeable. Acetazolamide has a role in treating CME due to RP.

- **CME DUE TO OTHER SURGERY LIKE RD SURGERY, PKP**

There is a 40% incidence of CME in aphakic eyes undergoing RD surgery and 25% in phakic eyes. There is 40% incidence following PKP.

SEQUELAE OF CME

Permanent macular degeneration may arise secondary to prolonged chronic CME. The cystoid spaces of the macula may coalesce together so that all retinal elements disappear except for the ILM. After the ILM also disintegrates, a lamellar hole is formed which may be one fourth to one third disc diameter in size. In the presence of lamellar hole, the visual acuity may continue to be good because of retention of some percipient elements.

BIOMICROSCOPY OF LAMELLAR HOLE

It is sometimes difficult to differentiate from a large foveal cystoid space with the ILM intact. The degenerative macular hole has gradual sloping margins and irregular edges. The border later becomes well defined by 4 months to one year.

PART - II

AIM OF THE STUDY

To study the epidemiology of cystoid macular edema and analyse the effectiveness of intravitreal triamcinolone acetonide in treatment of refractory cystoid macular edema.

PRIMARY OBJECTIVES

1. To study the epidemiology of refractory cystoid macular edema.

2. To study the effectiveness of intravitreal triamcinolone acetonide in treatment of refractory cystoid macular edema in terms of visual acuity and central macular thickness.

SECONDARY OBJECTIVES

1. To evaluate safety of intravitreal injection of triamcinolone acetonide.

INCLUSION CRITERIA

1. Central macular thickness on OCT more than 300µm.

2. Refractory diffuse diabetic macular edema not responding to grid laser photocoagulation.

3. Refractory pseudophakic cystoid macular edema not responding to topical anti-inflammatory drugs and grid laser photocoagulation.

4. Cystoid macular edema due to vein occlusions that was refractory to grid laser photocoagulation.

5. Patients who accepted treatment and had a follow up period of at least 12 weeks.

EXCLUSION CRITERIA

1. Patients with history or signs of uveitis.

2. Patients with other pre-existing macular degenerations due to causes like ARMD, RP, etc.

3. Patients with aphakic CME and pseudophakic CME with complications like pupillary capture, subluxated IOL, vitreous incarceration at wound site needing surgical correction.

4. Patients with CME following other surgical procedures like RD surgery, Combined surgery, Penetrating keratoplasty, etc.

5. Patients with history of glaucoma or ocular hypertension.

6. Patients on systemic corticosteroid therapy.

7. Patients with Vitreomacular traction or taut posterior hyaloid on OCT.

REFRACTORY MACULAR EDEMA

- In this study, all diabetic patients received atleast 2 sessions of laser photocoagulation according to ETDRS guidelines, and last laser treatment was atleast 4 months before IVTA treatment. All eyes considered for IVTA had residual retinal thickening with visual acuity less than 6/18 on Snellen's chart and macular thickness more than 300µm by OCT.

- All eyes of vein occlusion induced macular edema received laser photocoagulation and which were refractory to treatment with central macular thickness more than 300µm.

- All eyes that presented with pseudophakic cystoid macular edema that were refractory to topical anti-inflammatory drugs and grid laser photocoagulation and central macular thickness more than 300µm.

MATERIALS AND METHODS

This prospective study was carried out at Regional institute of ophthalmology, Chennai in Vitreo-retina clinic from November 2011 to November 2013. Patients who were referred to Vitreo-retina clinic with a provisional diagnosis of diabetic macular edema, pseudophakic CME, BRVO, CRVO were screened and selected for study.

40 eyes of 32 patients were evaluated in terms of detailed history regarding onset, duration, presenting symptoms, about previous surgery details and treatment of eye in past and systemic conditions like diabetes, hypertension.

All patients were subjected to detailed systemic and ophthalmic evaluation. Relevant systemic investigations like FBS, PPBS, BP were done.

Best corrected visual acuity was recorded with Snellen’s chart. Anterior segment examination was done with slit lamp regarding presence of any signs of uveitis, to look for lens status- phakic or pseudophakic, position of IOL and any complications like pupillary capture, subluxation of IOL, vitreous in wound site.

Posterior segment examination was done using slitlamp biomicroscopy with +90 D lens and indirect ophthalmoscope. Fundus photograph was taken in all cases for documentation. Fundus fluorescein angiography was done in all cases to look for flower petal leakage from perifoveal capillaries in macular region. Optical coherence tomography was done in all cases to look for type of macular edema, central macular thickness. Intraocular pressure was noted in all cases with Goldmann applanation tonometry.

All patients who had cystoid spaces in macular region on OCT, who were refractory to treatment like grid and focal laser photocoagulation in vascular causes and topical anti-inflammatory drugs and grid laser photocoagulation in pseudophakic cases were subjected to treatment with intravitreal triamcinolone acetonide injection.

A commercially available Triamcinolone acetonide without preservative (CORTEYE 40mg/ml) is available. Under aseptic techniques using 5% povidone iodine and topical antibiotics, 4mg in 0.1ml of triaminolone acetonide was injected intravitreally in superotemporal quadrant via parsplana. After injection, intraocular pressure and central retinal artery perfusion was checked. Patients were instructed to administer topical antibiotics for 1 week.

FOLLOW UP

Patients were followed up on first postoperative day following intravitreal injection. They were followed up at the end of first week, 4 weeks, 8weeks and 12 weeks. At each visit anterior segment examination by slit lamp biomicroscopy, intraocular pressure with Goldmann applanation tonometry, visual acuity recording with Snellen's chart and fundus examination by +90 D was done. A repeat OCT was done at 8weeks and 12weeks to look for central macular thickness.

If the patient however presents with pain, ocular redness, decrease in visual acuity, they were instructed to contact ophthalmologist immediately.

The results published here are for a period of follow up extending upto six months.

GUIDELINES FOR INTRAVITREAL INJECTION

1. Povidone iodine application for ocular surface, eyelid and eyelashes.
2. Use of eye speculum and avoid contamination of the needle with eyelid margin.

3. Avoid extensive massage of eyelids both pre and post injection.
4. Adequate use of topical anaesthetics.
5. Avoid prophylactic and post injection paracentesis.
6. Intraocular pressure to be checked following injection.
7. Dilated fundoscopic examination should be done following injection to look for central retinal artery perfusion and intraocular location of the drug.

MAIN OUTCOME MEASURES

1. Best corrected visual acuity (logMAR conversion of Snellen's chart)
2. Central macular thickness (µm) with OCT.
3. Intraocular pressure (mm Hg) measurement with Goldmann's applanation tonometry.

STATISTICAL ANALYSIS

Data analysis was carried out by the Statistical Package For Social Science (SPSS). Paired t-test was done to analyse the central macular thickness before and after intervention. Pearson's correlation coefficient was done to find out the correlation between macular thickness and visual acuity.

INTRAVITREAL TRIAMCINOLONE ACETONIDE INJECTION

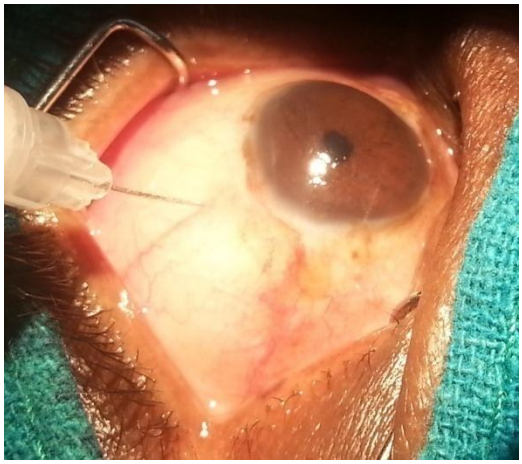


FIGURE: These pictures depict administration of Triamcinolone acetonide intravitreally through parsplana route.

ANALYSIS AND RESULTS

1. AGE DISTRIBUTION

Total patients enrolled in our study is 32.

Table - 1

Age (in years)	No.of patients	Percentage
31 -40	2	6.25%
41-50	4	12.5%
51-60	12	37.5%
61-70	12	37.5%
71-80	2	6.25%

Majority of patients in this study were in the age group of 51-70 years (75%). The mean age of presentation was 58.53 ± 9.59 years. The oldest patient was 73 years and the youngest was 33 years.

2. SEX DISTRIBUTION

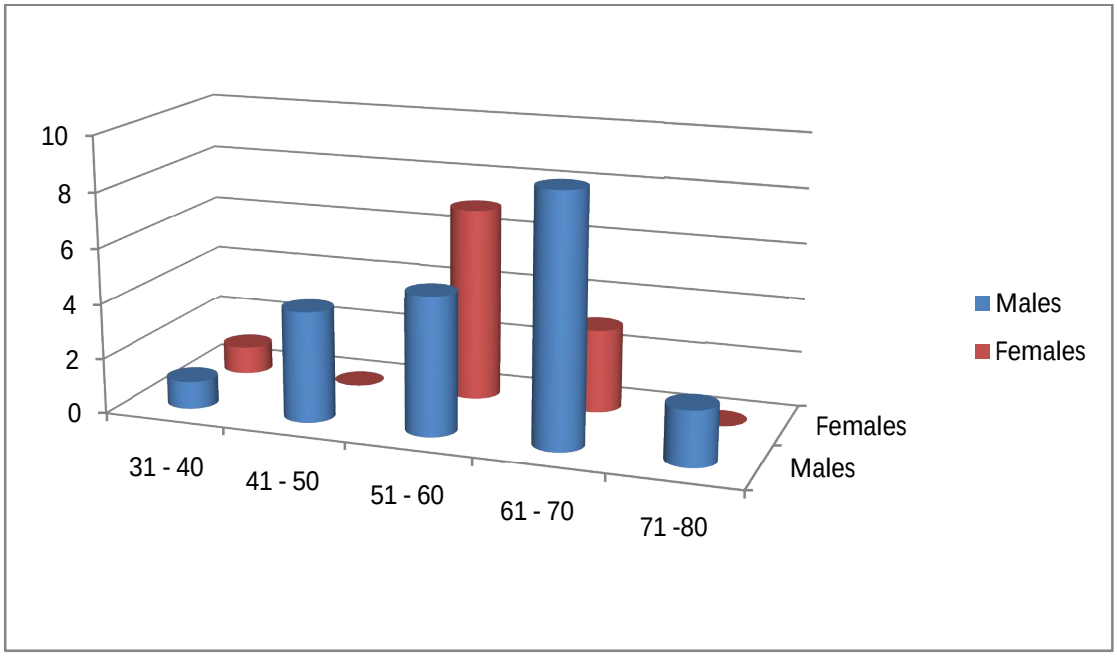
Table - 2

Sex	No. of patients	Percentage
MALE	21	65.63%
FEMALE	11	34.38%

In this study, there was a slight male preponderance, males accounting for 65.63% of patients. Majority of them were in 61 -70 years age group.

CHART - 1

AGE AND SEX DISTRIBUTION



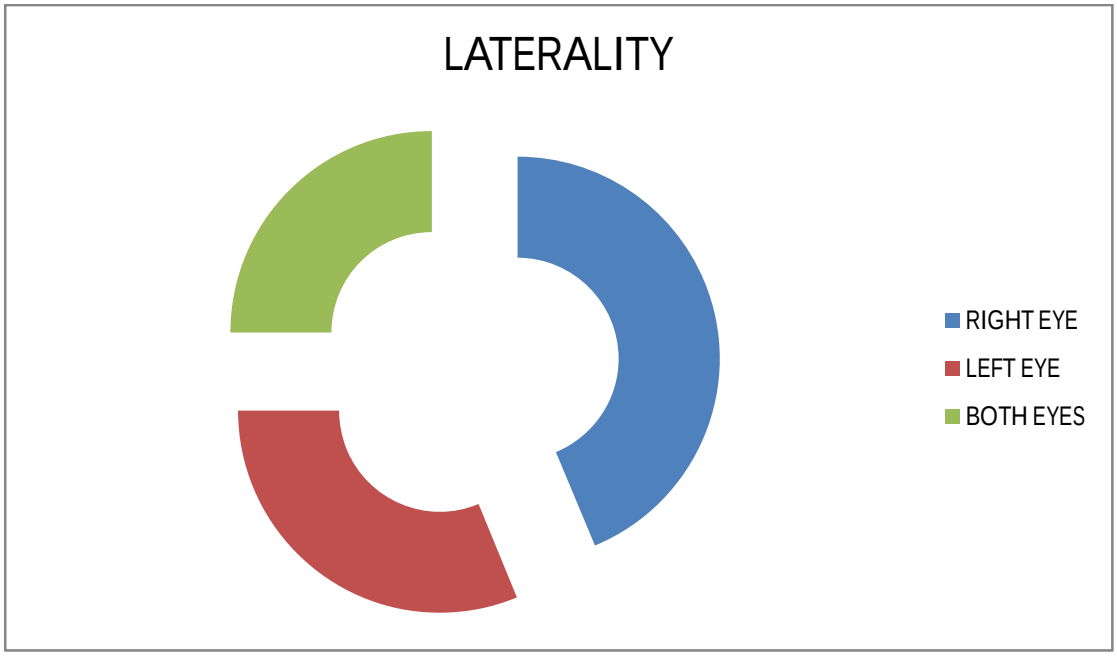
3. LATERALITY

Table - 3

Eye	No. of patients	Percentage
RIGHT	14	43.75%
LEFT	10	31.25%
BOTH	8	25%

In this study, incidence of cystoid macular edema was more in right eye (43.75%). In 8 cases (25%) there was a bilateral presentation.

CHART 2



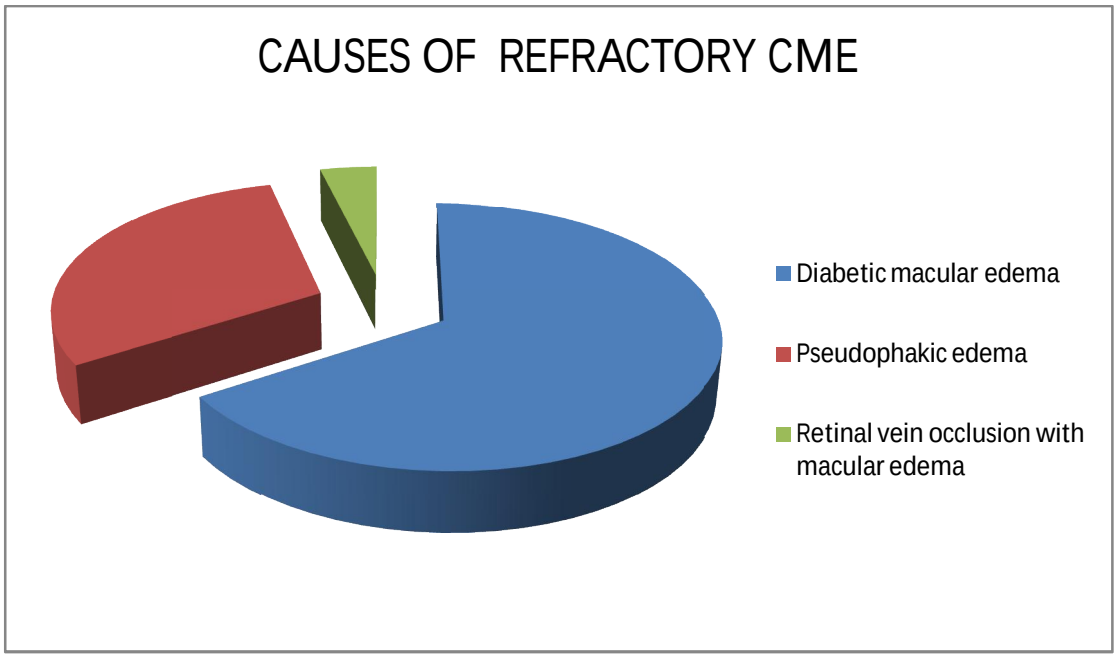
4. CAUSES OF REFRACTORY CYSTOID MACULAR EDEMA

Table -4

Cause	No. of eyes	Percentage
DIABETIC MACULAR EDEMA	24	60%
PSEUDOPHAKIC MACULAR EDEMA	11	27.5%
RETINAL VEIN OCCLUSION WITH CME	5	12.5%

In this study, Diabetic macular edema accounted for 60% , Pseudophakic macular edema for 27.5% , Retinal vein occlusion macular edema for 12.5%.

CHART - 3



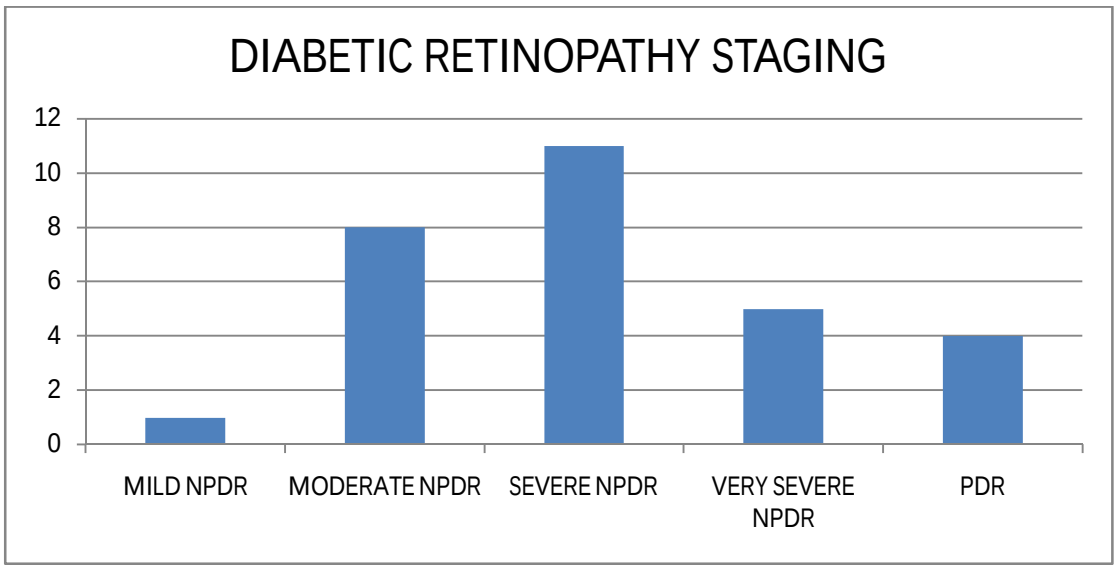
5. ASSOCIATION OF DIABETES WITH CME

Table - 5

Stage of diabetic retinopathy	No. of eyes	Percentage
MILD NPDR	1	3.45%
MODERATE NPDR	8	27.59%
SEVERE NPDR	11	37.93%
VERY SEVERE NPDR	5	17.24%
PDR	4	13.79%
TOTAL	29	100%

Out of 40 CME eyes, 29 eyes were diabetic. Of which, severe NPDR (11 eyes) contributed to 37.93%, moderate NPDR(8 eyes) contributed to 27.59%, very severe NPDR (5 eyes) contributed to 17.24%, PDR (4 eyes) contributed to 13.79%, mild NPDR (1 eye) contributed to 3.45%. About 11 eyes had no diabetic retinopathy.

CHART - 4



6. DATA ANALYSIS IN DIABETIC MACULAR EDEMA

Table 6

PRE TREATMENT MACULAR THICKNESS

Macular Thickness	No.of eyes	Percentage
300 – 400 µ	3	12.5%
400 – 600 µ	8	33.4%
600 – 800 µ	6	25%
800 – 1000 µ	5	20.8%
>1000 µ	2	8.3%

The mean pre treatment macular thickness is 670.38 ± 216.27µm, (S.E-44.14).

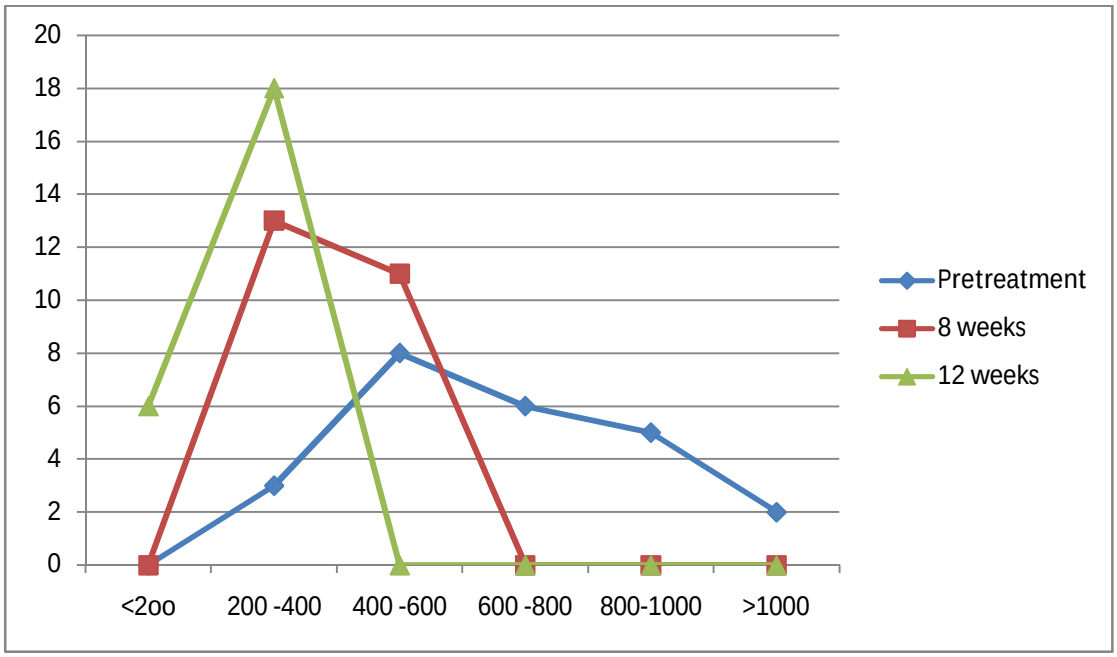
Table 7

POST TREATMENT MACULAR THICKNESS

Macular Thickness	8 Weeks		12 Weeks	
	No. of eyes	%	No. of eyes	%
< 200 µ	0	0%	6	25%
200 – 400 µ	13	54.17%	18	75%
400 – 600 µ	11	45.83%	0	0%
600 – 800 µ	0	0%	0	0%
8000 – 1000 µ	0	0%	0	0%
>1000 µ	0	0%	0	0%

CHART - 5

Comparison of Pre and Post Treatment Macular Thickness in DME



The mean macular thickness at 8 weeks and 12 weeks post intervention were 385.46 ± 90.31 µm (S.E – 19.02) and 247.25 ± 58.41 µm (S.E – 11.92) respectively.

Paired t test showed the two tailed 'p' value is **<0.0001** which means there is a **significant** difference in central macular thickness before and after IVTA at 8 weeks as well as 12 weeks.

The mean reduction in macular thickness at 8 weeks and 12 weeks post intervention were 285.25 ± 158.07 µm (S.E – 32.27) and 423.13 ± 196.55 µm (S.E – 40.12) respectively.

VISUAL ACUITY

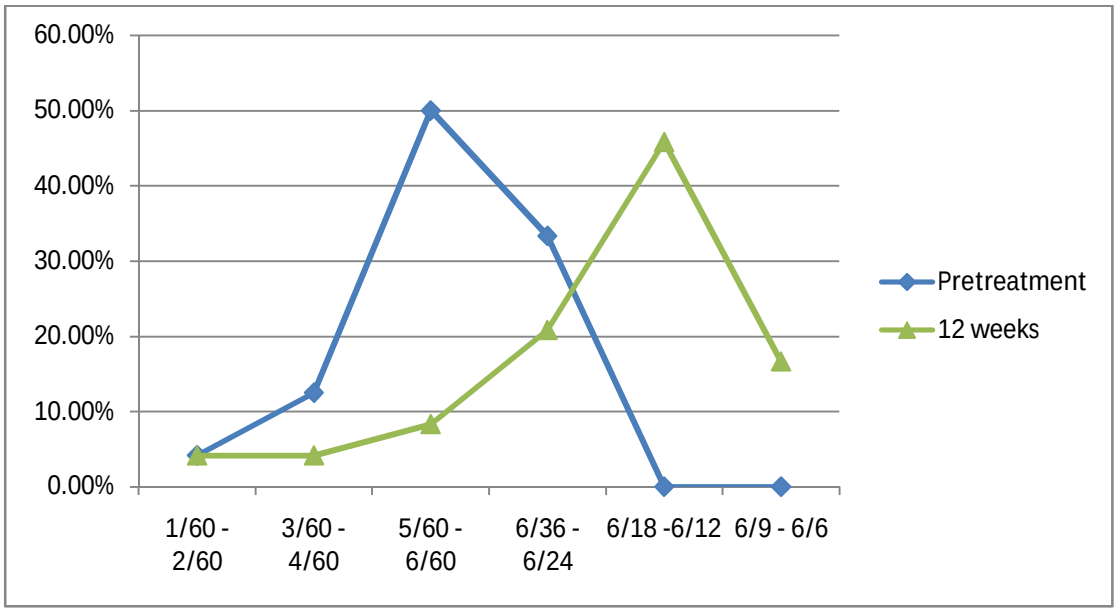
Table - 8

Visual acuity	Pre Treatment		Post Treatment at 12 Weeks	
	No.of eyes	%	No.of eyes	%
1/60 – 2/60	1	4.17%	1	4.17%
3/60 – 4/60	3	12.5%	1	4.17%
5/60 - 6/60	12	50%	2	8.33%
6/36 – 6/24	8	33.33%	5	20.83%
6/18 – 6/12	0%	0%	11	45.83%
6/9 – 6/6	0	0%	4	16.67%

After logMAR conversion , mean visual acuity was found to be 0.98 (6/60) ± 0.21 before IVTA and 0.52 (6/18) ± 0.34 after IVTA. In paired t-test, ‘p’ value was **<0.0001** which signifies the improvement in visual acuity.

CHART - 6

Comparison between Pre and Post Treatment Visual acuity in DME

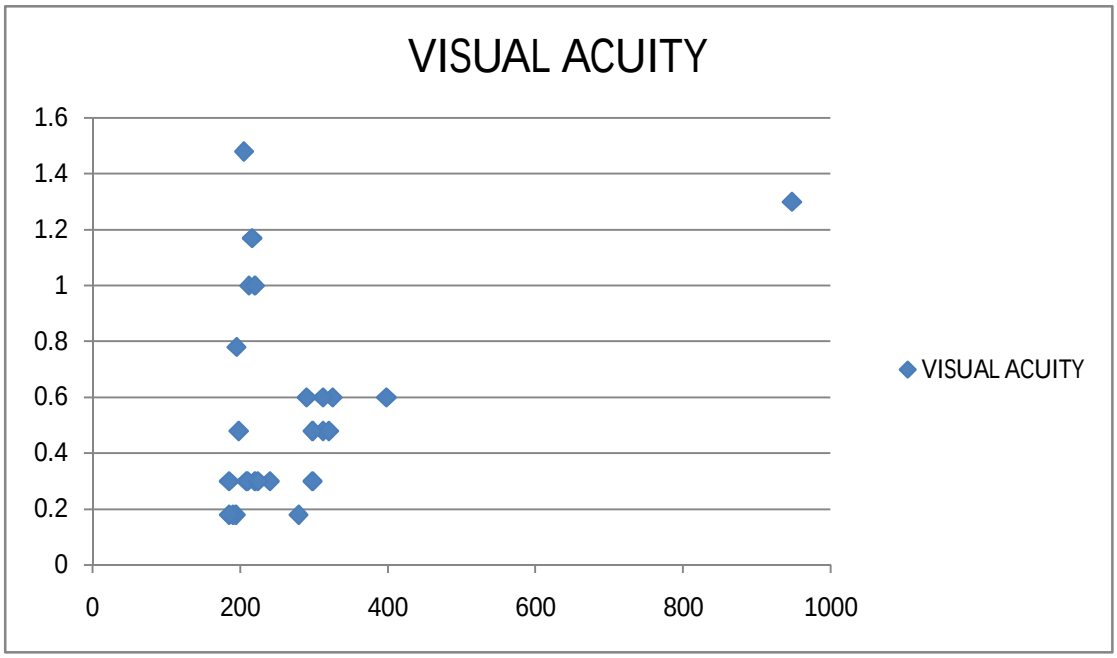


All patients in my study presented with visual acuity between 2/60 - 6/24. Majority of them had 6/36 – 6/24 (58.3%). After treatment with IVTA, at 8 weeks, 54.17% of patients gained vision upto 6/18 – 6/12. At 12 weeks, 4 out of 24 cases (16.67%) gained 6/9 vision and 11 out of 24 cases (45.83%) gained vision upto 6/12. Only 4 cases (16.67%) did not regain significant visual improvement and were less than 6/60.

CORRELATION BETWEEN MACULAR THICKNESS AND VISUAL ACUITY

By Pearson's correlation coefficient, ‘r’ value was 0.61 suggesting a **MODERATELY POSITIVE** correlation between macular thickness and visual acuity before treatment whereas ‘r’ value post treatment(12 weeks) was -0.01 suggesting a weakly negative correlation between the same.

CHART - 7



This chart explains the correlation between macular thickness and visual acuity post IVTA in Refractory DME.

7. DATA ANALYSIS IN PSEUDOPHAKIC EDEMA

PRE TREATMENT MACULAR THICKNESS

Table 9

Macular Thickness	No.of Eyes	Percentage
300 – 400 µ	0	0%
400 – 600 µ	2	18.1%
600 – 800 µ	4	36.4%
800 – 1000 µ	5	45.5%
>1000 µ	0	0%

The mean macular thickness before treatment is 763.45 ± 148.57µm (SE-44.71).

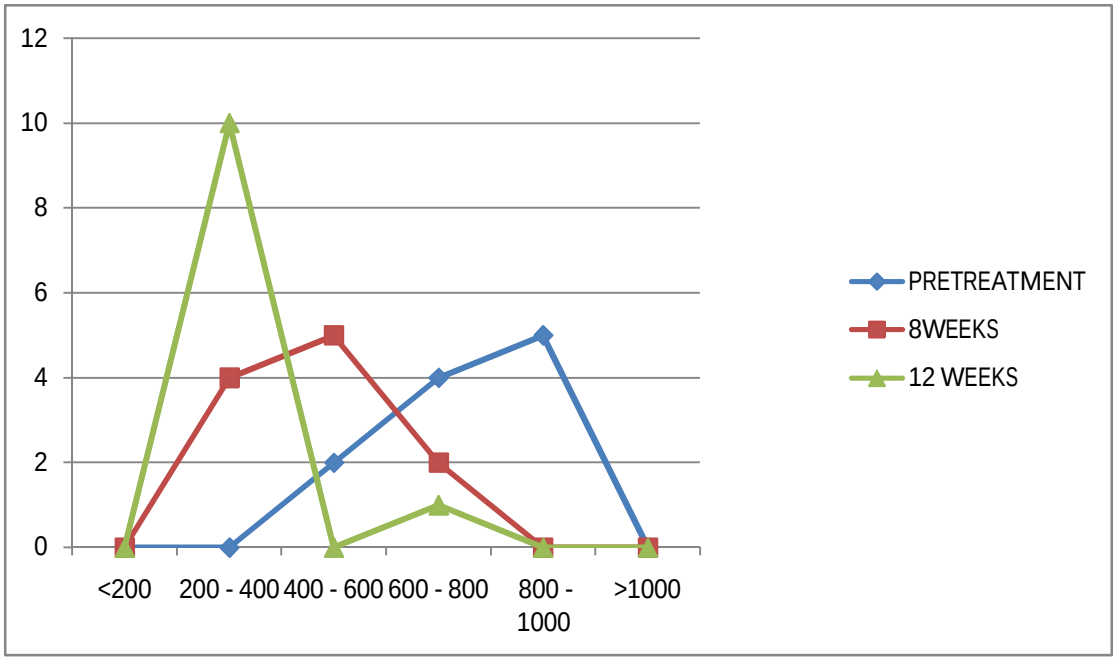
POST TREATMENT MACULAR THICKNESS

Table 10

Macular Thickness	At 8 Weeks		At 12 Weeks	
	No.of eyes	%	No.of eyes	%
< 200 µ	0	0%	0	0%
200 – 400 µ	4	36.36%	10	90.09%
400 – 600 µ	5	45.45%	0	0%
600 – 800 µ	2	18.18%	1	9.09%
8000 – 1000 µ	0	0%	0	0%
>1000 µ	0	0%	0	0%

Comparison of Pre and Post Treatment Macular Thickness in Pseudophakic CME

Chart - 8



The mean macular thickness after treatment at 8 weeks is 486.18 ± 123.53µm (SE-38.75) and at 12 weeks is 312.55 ± 119.41µm(SE-36.00).

Paired t test showed the two tailed 'p' value is **<0.0001** which means there is a **significant** difference in central macular thickness before and after IVTA at 8 weeks as well as 12 weeks.

The mean reduction in macular thickness at 8 weeks and 12 weeks post intervention were 276.91 ± 89.53 µm (S.E – 26.99) and 450.55 ± 126.40 µm (S.E – 38.11) respectively.

POST TREATMENT VISUAL ACUITY

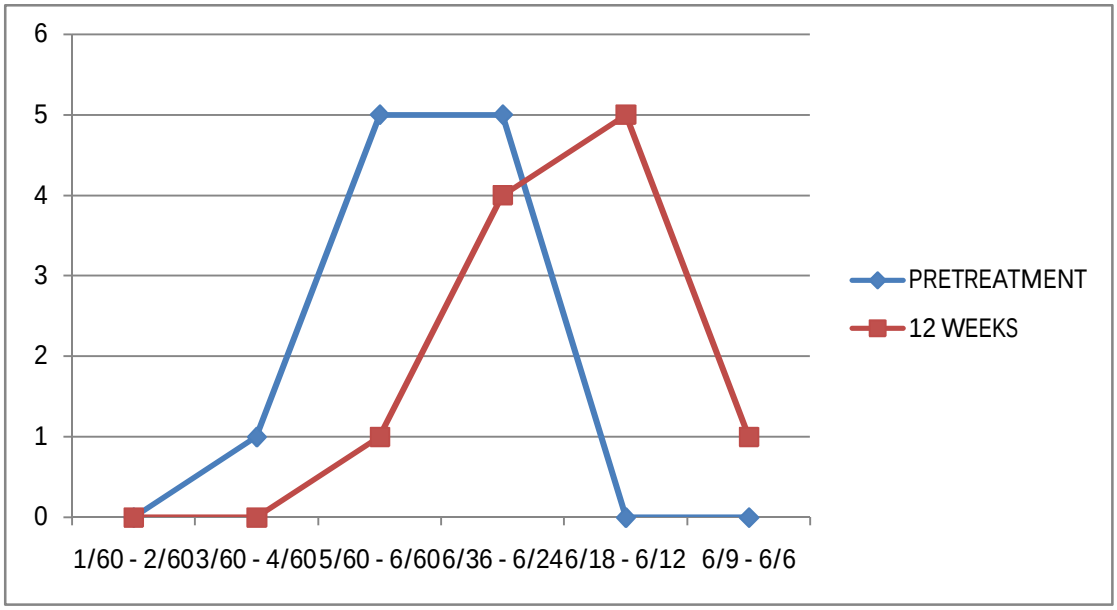
Table 11

Visual Acuity	Pre Treatment		Post Treatment - 12 Weeks	
	No. of eyes	%	No. of eyes	%
1/60 – 2/60	0	0%	0	0%
3/60 – 4/60	1	9%	0	0%
5/60 - 6/60	5	45.50%	1	9.09%
6/36 – 6/24	5	45.50%	4	36.36%
6/18 – 6/12	0	0%	5	45.46%
6/9 – 6/6	0	0%	1	9.09%

After logMAR conversion , mean visual acuity was found to be 0.87 (6/36) ± 0.21 before IVTA and 0.53(6/18) ± 0.26 after IVTA. In paired t-test, ‘p’ value = **0.0003** which signifies the improvement in visual acuity.

Comparison of Pre and Post Treatment Visual acuity Improvement in Pseudophakic CME

Chart - 9

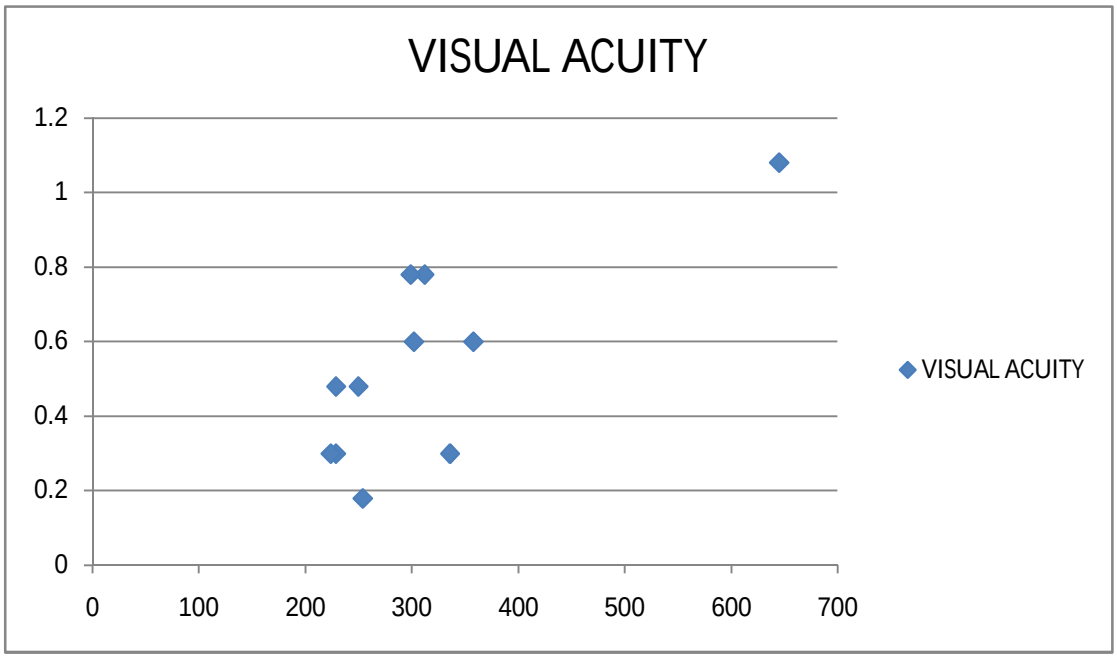


All patients in my study presented with visual acuity between 2/60 - 6/24. Majority of them had 5/60 – 6/24 (91%). After treatment with IVTA, at 8 weeks, 54.55% of patients gained vision upto 6/18 – 6/12. At 12 weeks, 5 out of 11 cases (45.46%) gained 6/12 vision. 1 case regained vision upto 6/9. 1 case (9.09%) did not regain significant visual improvement and was less than 6/60 due to hole formation.

CORRELATION BETWEEN MACULAR THICKNESS AND VISUAL ACUITY

By Pearson's correlation coefficient, ‘r’ value was 0.46 suggesting a **WEAK POSITIVE** correlation between macular thickness and visual acuity before treatment whereas ‘r’ value post treatment(12 weeks) was 0.72 suggesting a **STRONG POSITIVE** correlation between the same.

CHART - 10



This chart explains the correlation between macular thickness and visual acuity post intervention in Pseudophakic CME.

8. DATA ANALYSIS IN RETINAL VEIN OCCLUSION MACULAR EDEMA

PRE TREATMENT MACULAR THICKNESS

Table 12

Macular Thickness	No.of Eyes	Percentage
300 – 400 µ	2	40%
400 – 600 µ	1	20%
600 – 800 µ	2	40%
800 – 1000 µ	0	0%
>1000 µ	0	0%

The pre treatment mean macular thickness is 541.2 ± 183.97µm (SE -82.28).

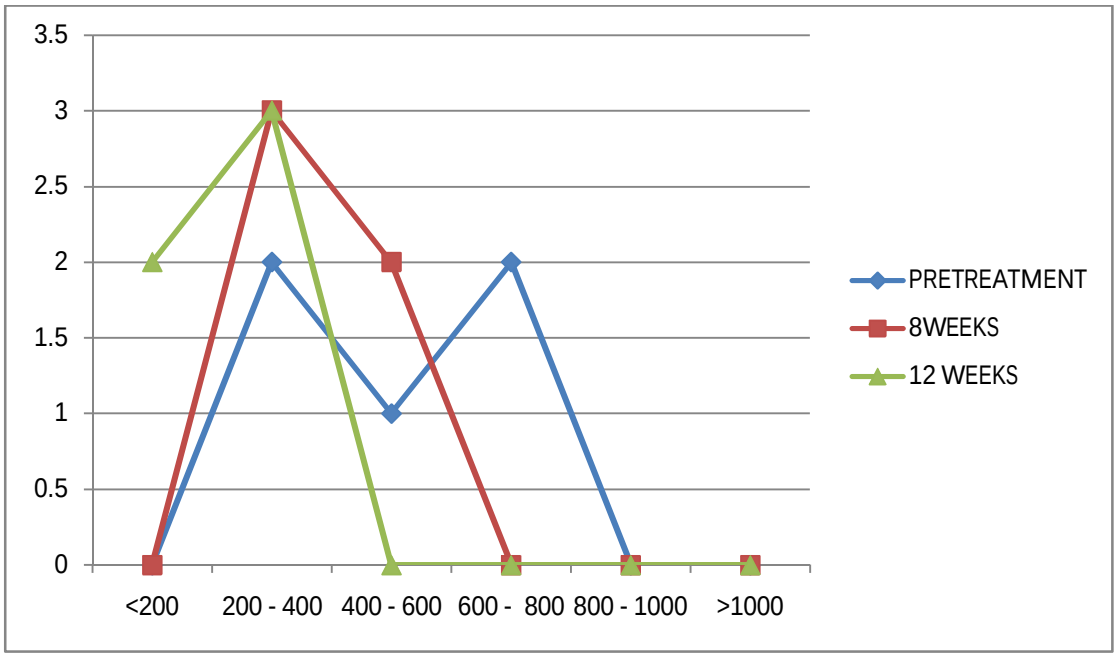
POST TREATMENT MACULAR THICKNESS

Table 13

Macular Thickness	At 8 Weeks	At 12 Weeks
< 200 µ	0	2
200 – 400 µ	3	3
400 – 600 µ	2	0
600 – 800 µ	0	0
8000 – 1000 µ	0	0
>1000 µ	0	0

Comparison of Pre and Post Treatment Macular Thickness in Retinal Vein Occlusion Macular Edema

CHART - 11



The mean macular thickness post treatment at 8 weeks and 12 weeks were 381.6 ± 150.30µm (SE– 67.22) and 222.8 ± 42.83µm (SE-19.16).

Paired t test showed that there is a **significant** difference in central macular thickness before and after IVTA at 8 weeks & 12 weeks, ‘ p’ values being 0.0179, 0.009 respectively.

The mean reduction in macular thickness at 8 weeks and 12 weeks post intervention were 276.91 ± 89.53 µm (S.E – 26.99) and 450.55 ± 126.40 µm (S.E – 38.11) respectively.

VISUAL ACUITY

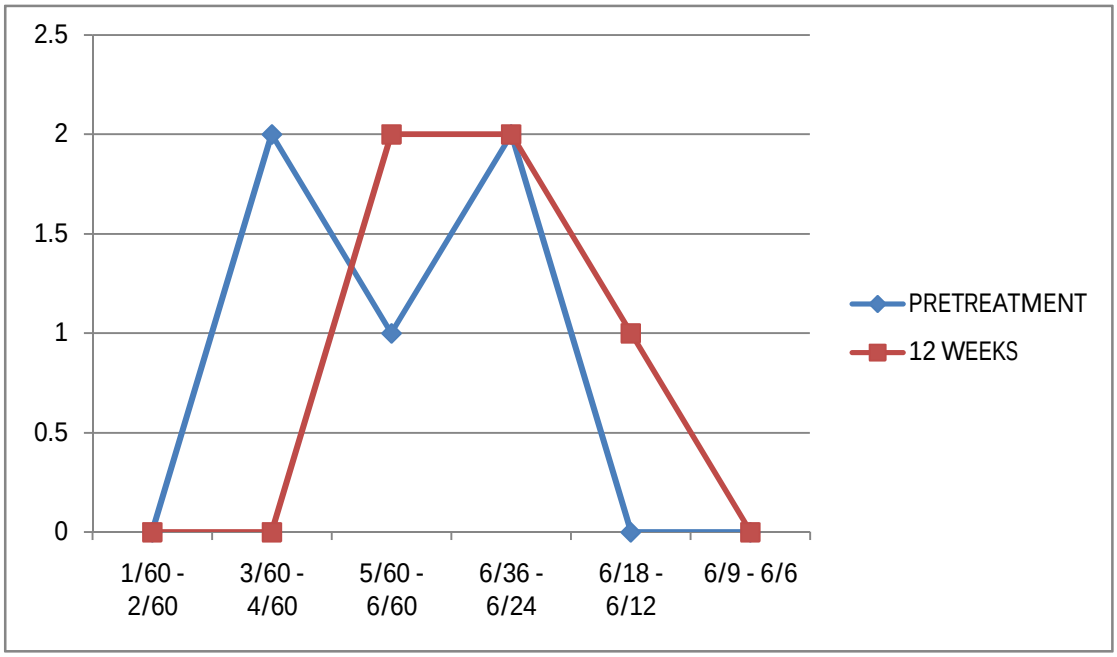
Table 14

Visual Acuity	Pre Treatment		Post Treatment At 12 Weeks	
	No.of eyes	%	No.of eyes	%
1/60 – 2/60	0	0%	0	0%
3/60 – 4/60	2	40%	0	0%
5/60 - 6/60	1	20%	2	40%
6/36 – 6/24	2	40%	2	40%
6/18 – 6/12	0	0%	1	20%
6/9 – 6/6	0	0%	0	0%

After logMAR conversion, mean visual acuity was found to be 0.97 (6/60) ± 0.28 before IVTA and 0.70(6/36) ± 0.3 after IVTA. In paired t-test, 'p' value = **0.0084** which signifies the improvement in visual acuity.

Comparison of Pre and Post Treatment Visual acuity Improvement in Retinal Vein Occlusion Macular Edema

CHART - 12

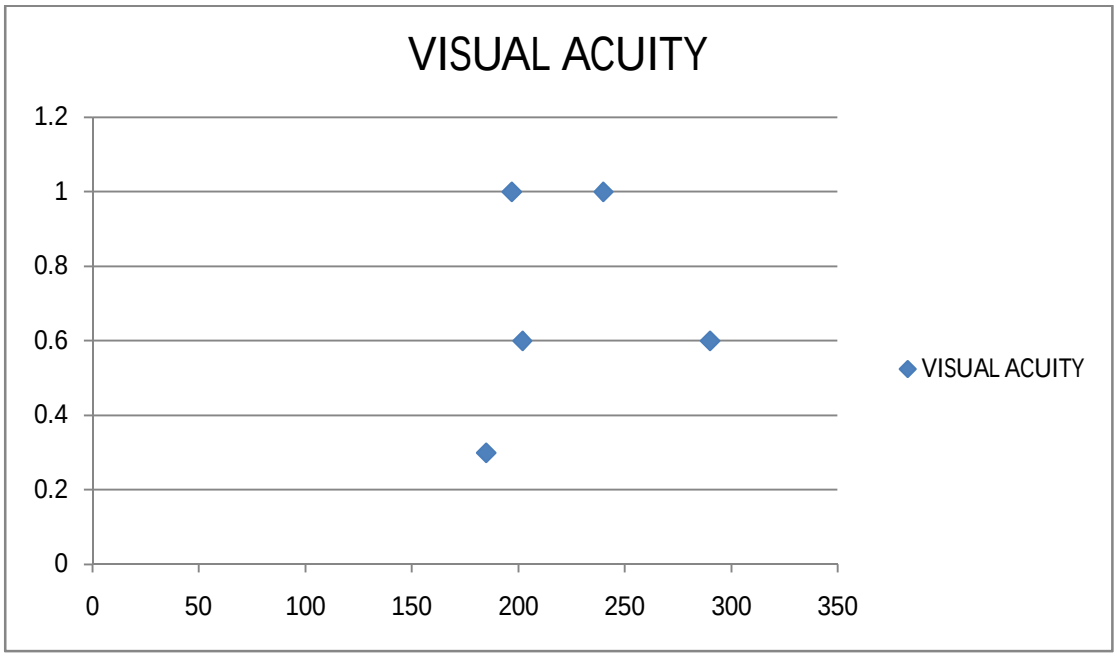


All patients in my study presented with visual acuity between 3/60 - 6/24. After treatment with IVTA, at 8 weeks, 1 patient gained vision upto 6/18 – 6/12. At 12 weeks, the same patient retained his 6/12 vision. Due to longstanding macular edema, average of 1 snellen line visual improvement only was noted.

CORRELATION BETWEEN MACULAR THICKNESS AND VISUAL ACUITY

By Pearson's correlation coefficient, ‘r’ value was 0.62 suggesting a **MODERATE POSITIVE** correlation between macular thickness and visual acuity before treatment whereas ‘r’ value post treatment(12 weeks) was 0.15 suggesting a **WEAK POSITIVE** correlation between the same.

CHART -13



This chart explains the correlation between macular thickness and visual acuity post injection in retinal vein occlusion CME.

9. COMPARISON OF REDUCTION IN CENTRAL MACULAR THICKNESS AMONG THREE GROUP OF PATIENTS

Table - 15

Group	Frequency (No.of Eyes)	Mean CMT at 8 Weeks	Mean CMT at 12 Weeks
DME	24	285.25 ± 158.07	423.13 ± 196.55
Retinal vein occlusion CME	5	159.60 ± 64.58	318.40 ± 148.52
Pseudophakic CME	11	276.91 ± 89.53	450.55 ± 126.398

Maximum mean reduction in IOP was seen in Diabetic macular edema at 8 weeks. At the end of 12 weeks, Pseudophakic CME had a significant reduction in IOP.

10. INTRAOCULAR PRESSURE

Table - 16

IOP(mmHg)	No.of Eyes		
	Pretreatment	1 week	12 weeks
<12	2	3	2
12 -16	23	20	25
16 - 20	15	8	12
>20	0	9	1

The mean pre treatment IOP was 16.05 ± 2.14 mm Hg. The mean post treatment IOP at 1 week and 12 weeks respectively were 17.4 ± 3.93 mm Hg and 16.05 ± 2.29 mm Hg

Out of 40 eyes, 9 eyes showed a rise in IOP accounting for 22.5%. Of which 1 patient was refractory to treatment with topical antiglaucoma drugs and needed trabeculectomy and all others were manageable with topical anti glaucoma drugs.

DISCUSSION

- **AGE DISTRIBUTION**

In this study of 32 patients, majority of the patients (75%) belong to 5th and 6th decades. This may be due to the fact that most of cataract surgeries take place in this age group and prevalence of systemic diseases like DM and HT is more common in this age group. We had 6 cases below 50 years accounting for 18.75% of patients. Previous studies showed similar involvement. (Daniel M.Taylor et al.[21] Survey ophthalmology)

- **SEX DISTRIBUTION**

The study revealed a slight Male preponderance with a male to female ratio of 1.9:1.

- **LATERALITY**

In this study, RE (43.75%) was more commonly involved than LE(31.25%), bilateral(25%) presentation being uncommon relatively.

- **ETIOLOGY**

DIABETES shares the highest proportion of 60% followed by PSEUDOPHAKIA (27.5%), last being VEIN OCCLUSION(12.5%).

- **CME IN RELATION TO SURGICAL COMPLICATONS**

About 9 cases had posterior capsular rent and 2 cases had iritis in this study. A posterior capsular rent leads to loss of barrier effect, thus predisposing to develop CME. The increased association of CME with post op iritis has been well documented by Marvin L.Sears (Surv. Ophthalmol 28(suppl) :525-534,1984)[22] who states occurrence of CME after ocular trauma (surgery) is related to synthesis and release of endogenous mediators like prostaglandins.

About 33.3% (6 cases) developed CME despite an uncomplicated surgery and uneventful post operative period. This may be because of ocular trauma caused by surgery leading to synthesis of inflammatory mediators that lead diffuse posteriorly and also because of nonfunctioning of Bito's[23] pump in ciliary epithelium for 3 weeks post surgery. Some patients have an inherent predisposition for development of CME like DM, HT.

- **CME IN DIABETES MELLITUS**

Out of 40 eyes studied, 29 eyes suffered diabetic retinopathy of which 11 patients belonged to severe NPDR stage followed in order by moderate NPDR(8), very severe NPDR(5), PDR(4), mild NPDR(1).

- **ASSOCIATION OF PVD**

Out of 40 eyes, 11 eyes (27.5%) that had incomplete PVD and 7 eyes(22.5%) with complete PVD on OCT. A total of 18 eyes accounting for 45% had either complete or incomplete PVD. Remaining 22 eyes(55%) did not have PVD.

Following cataract extraction, loss of hyaluronic acid from vitreous gel occurs, which accelerates vitreous degeneration. Combined with forward movement of vitreous body as a result of removal of crystalline lens, the loss of hyaluronic acid precipitates vitreous detachment. Firm attachments of vitreous cortex to retina are usually present at macula and optic disc. These normal vitreoretinal adhesions become focal sites of vitreoretinal traction when a PVD occurs predisposing to CME. A study by Schepens CL et al.(Ophthalmology 96 (10) : 1511-6,1989 Oct.)[24] gives a 42.1% incidence of PVD in patients with postoperative CME.

- **IVTA AND MACULAR THICKNESS**

In a country like India with high number of diabetics, visual morbidity due to DME is very high. Intravitreal triamcinolone acetonide is a promising therapeutic method for diabetic macular edema. As of current practice, according to ETDRS, laser photocoagulation is advocated for DME. However refractory edema can be treated with intravitreal Triamcinolone. Studies focused on macular edema that failed to respond to conventional laser photocoagulation (Martidis[25] et al., Karacorlu[26] et al., Audren[27] et al., Gilles[28] et al., ophthalmology 2006) stated that IVTA is effective in improving vision, reducing macular thickness and inducing reabsorption of hard exudates in diffuse diabetic macular edema.

In cases of macular edema due to venous occlusions, the recently concluded SCORE[31] study clearly mentions the benefit of IVTA as compared to standard therapy in CRVO. In BRVO, Triamcinolone and Grid laser shows a comparable response, however triamcinolone can be used for macular edema not responding to laser therapy.

In case of pseudophakic CME, Boscia[29] et al., states that reduction in mean macular thickness from 517.29 ± 146.98 µm to 263.71 ± 83.13 µm at 3 months of followup.

There was a significant reduction (statistically proven by paired t-test) in central macular thickness in all three groups both at 8 weeks and 12 weeks follow up period. Maximum reduction in macular thickness at 8 weeks was observed in diabetic group(285.25±158.07) whereas after 12 weeks follow up period, the reduction was highest in the pseudophakic group(450.55±126.398).

- **VISUAL ACUITY**

In DME, visual acuity showed a significant improvement from 6/60 before intervention to 6/24 after intervention which means an average two Snellen line improvement.

In pseudophakic CME, patients showed an average 2 Snellen line visual improvement which is significant (6/36 to 6/18).

In venous occlusion, visual acuity improvement was significant as in other groups, which was an average one snellen line improvement from 6/60 to 6/36.

- **INTRAOCULAR PRESSURE**

9 eyes of total 40 eyes (22.5 %) showed an increase in intraocular pressure on immediate post operative day and 1 week follow up. But 6 out of 7 cases were responded well to topical antiglaucoma drugs. However in my study, 1 case was refractory to topical medications and required antiglaucoma surgery to control IOP. Recent studies (Rhee[30] et al., Boscia[29] et al.) found a 35% and 57% increase in IOP following IVTA in follow up weeks controlled by topical medications.

- **CATARACT**

A recent study by Gillies[28] et al., has demonstrated that steroid related cataracts are more likely to form in patients who are steroid responders. In this study , as the follow up period was only 6months, and lens changes were not excluded in the beginning, progression of lens changes could not be assessed.

- **RECURRENCE OF MACULAR EDEMA**

Massin[27] et al., looked at patients unresponsive to laser photocoagulation and found a significant difference between CMT of eyes injected with 4mg IVTA and control eyes but effect was no longer

significant at 24 weeks because of recurrence of macular edema. This transient reduction in CMT correlated also to visual acuity.

In this study, about 50% eyes needed a repeat injection of IVTA who had a follow up of over 6 months due to weaning effect of the drug.

COMPLICATIONS

Refractory cases who did not show visual acuity improvement despite reduction in macular thickness had complications like ERM, Macular hole was seen in 7 eyes of total 40 eyes accounting for 17.5%.

SUMMARY

- This is a one year prospective , non randomized clinical study to evaluate the efficacy and safety of Intravitreal triamcinolone acetonide in treatment of refractory cystoid macular edema.
- The main aim was to evaluate the improvement in visual acuity and decrease in macular thickness in refractory cases like DME, pseudophakic CME, retinal venous occlusion CME.
- The occurence of adverse effects like increase in intraocular pressure were noted.
- In this study, 40 eyes of 32 patients were analysed and followed up for a period of 6 months.
- The mean age of presentation is 58.33 ± 9.5 years with a slight male preponderance with male : female ratio of 1.9 :1.
- Diabetes was found to be the leading causse (60%) followed in order by pseudophakia (27.5%) and venous occlusion (12.5%)

- Among various known complications, significant association of CME was found with posterior capsular rent and post operative iritis mediated by prostaglandins. About 33.3% of CME developed in uneventful intra and post operative period.
- Out of 40 eyes studied, 29 eyes suffered diabetic retinopathy, of which severe NPDR outnumbered other stages.
- This study supports previous reviews of literature stating a 50% association of PVD in CME eyes.

- **MACULAR THICKNESS**

Based on analysis of data available, there has been a substantial reduction in central macular thickness after IVTA administration during 8th and 12th week follow up in all three groups.

- **VISUAL ACUITY**

Visual acuity showed on an average of 2 Snellen line improvement in diabetic and pseudophakic CME and 1 Snellen line improvement, albeit, significant in venous occlusion CME.

Though visual acuity has improved in all 3 groups, it is not in correspondence with reduction in central macular thickness which can be

explained by photoreceptors derangement secondary to chronic macular edema.

- **INTRA OCULAR PRESSURE**

Intra ocular pressure risc noted in 22.5% eyes which responded well to topical antiglaucoma drugs in most cases. 1 case was refractory to medical therapy needing surgical intervention.

- **LIMITATIONS OF STUDY**

Lens changes (status) becomes a major confounding factor while analysing the complications of intravitreal Triamcinolone. This has not been addressed in the study.

While considering the weak correlation between reduction in macular thickness and visual acuity improvement, the possibilityof macular ischemia has to be ruled out which the study did not take into account.

Larger study group necessary to quantify the actual magnitude of benefit of this treatment modality with comparison to other therapies.

Longer follow up is necessary to document the post injection recurrences and progression of cataract.

CONCLUSION

Cystoid macular edema presented mostly in the 5th and 6th decade with slight male preponderance. This study describes diabetic retinopathy as the leading etiology with highest association with severe NPDR stage.

The fall in Mean macular thickness after IVTA was statistically significant in all three groups analysed. Etiology wise diabetic (423.13±196.55µm) and pseudophakic (450.55±126.398 µm) patients seem to be benefitted more than patients suffering from vein occlusion with greater reduction in mean macular thickness.

Among the three groups visual acuity improvement was on an average 2 Snellen line in diabetes and pseudophakic groups whereas in vein occlusion group was only 1 Snellen line improvement.

The correlation between Mean macular thickness and visual acuity pre treatment was moderate to strong positive in all 3 groups whereas there was a weak positive or neagative correlation post treatment due to underlying photoreceptor damage.

Intravitreal Triamcinolone acetonide is a promising therapy in refractory cystoid macular edema with established safety and effectiveness. Further study with a longer follow-up period and larger series is warranted to assess the treatment's long term efficacy and safety and the need for retreatment.

COMPARISON BETWEEN PRE AND POST TREATMENT MACULAR OCT

CASE REPORT -1

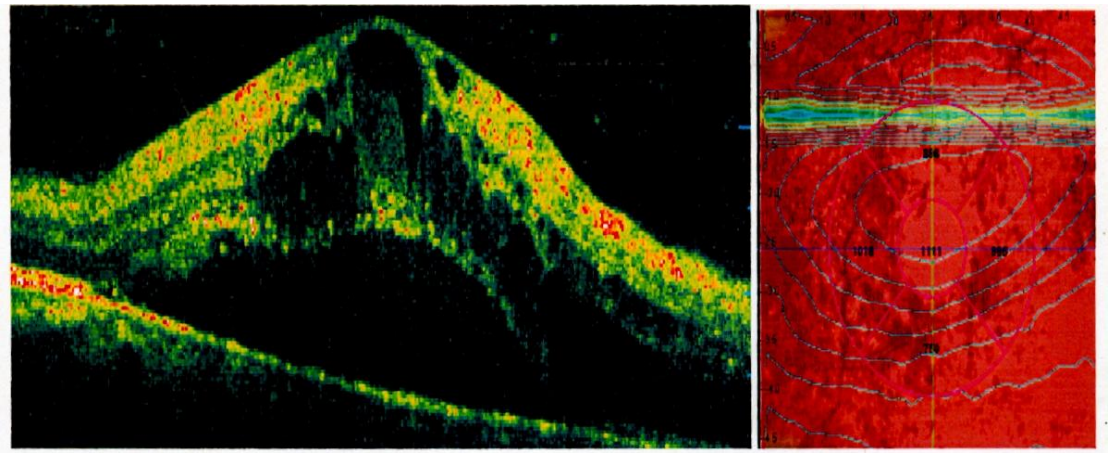


FIGURE 1: Pre injection: OCT shows cystoid spaces intraretinally with serous macular detachment. Central macular thickness is 1111µm.

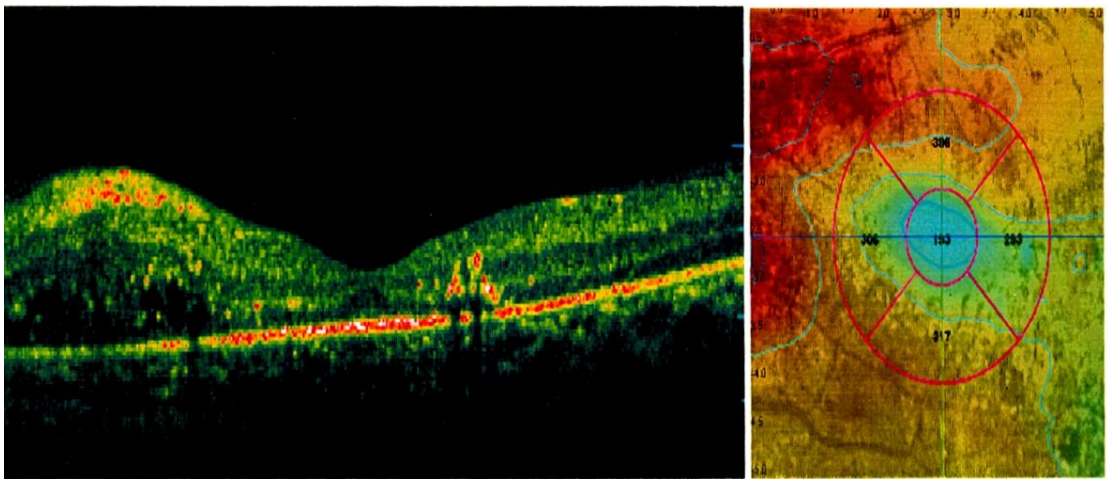


FIGURE 2: 12 Weeks Post injection: Repeat OCT shows reduction in cystoid spaces with macular thickness 183µm.

CASE - 2

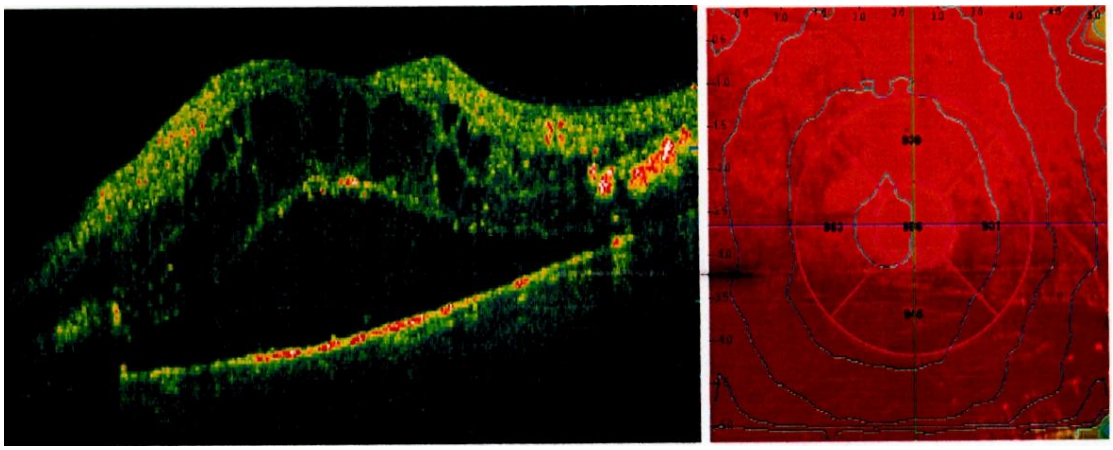


FIGURE 1: Pre injection cystoid change noted in the retina

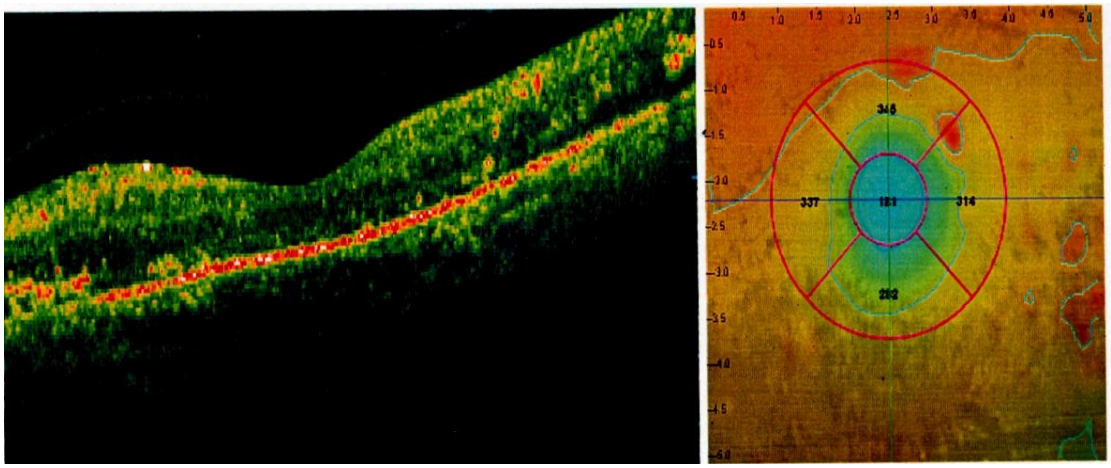


FIGURE 2: Post injection 12 weeks, cystoid edema has completely resolved with reduction in macular thickness. However visual acuity showed a minimal improvement by 1 line. The patient had a venous occlusion for about 1 year.

CASE – 3

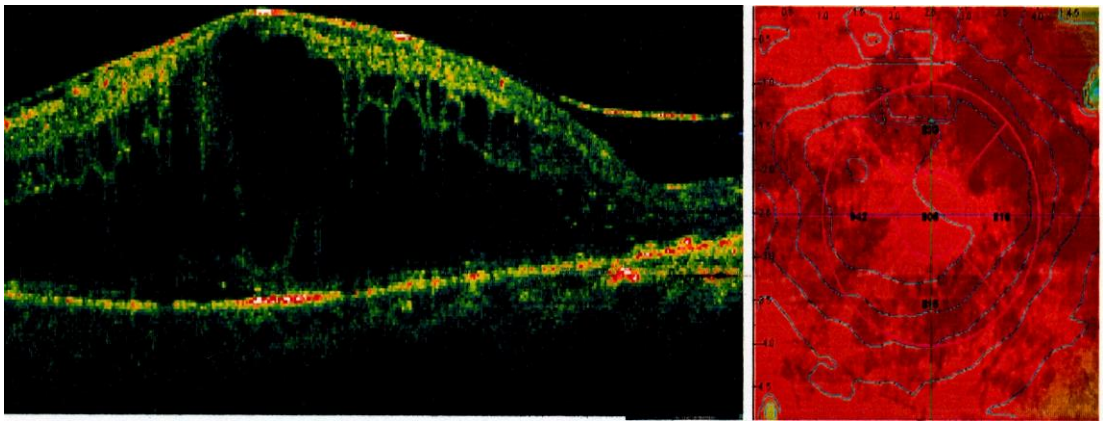


FIGURE 1: Pretreatment

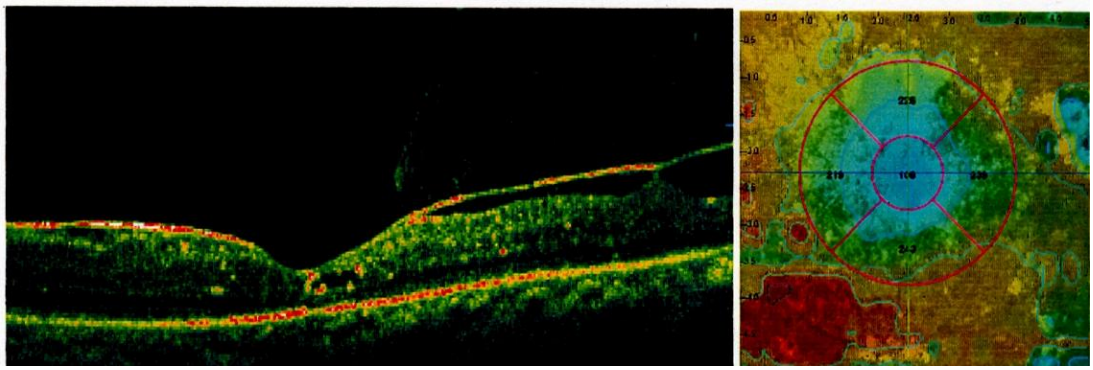


FIGURE 2: Post treatment 12 weeks showing a reduction in CMT

CASE – 4

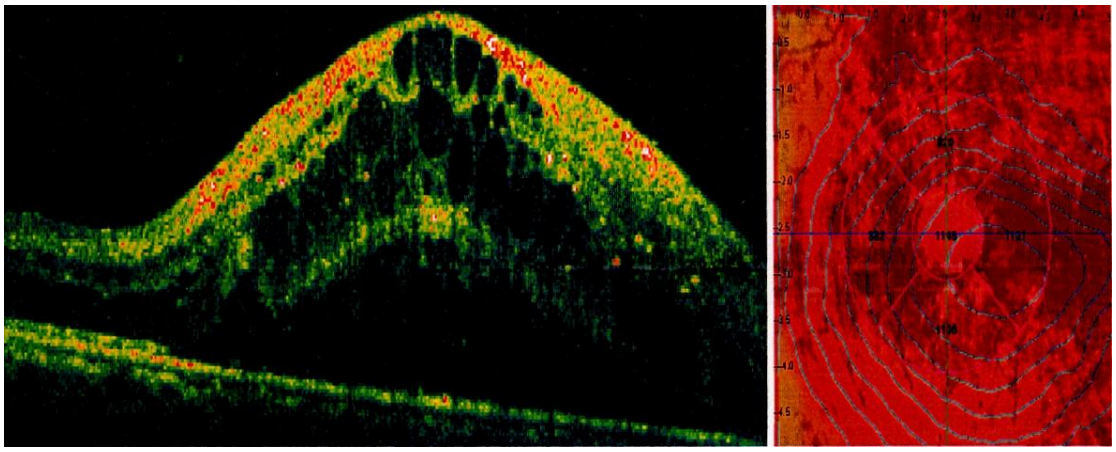


FIGURE 1: Pre injection: Multiple cystoid spaces with macular detachment

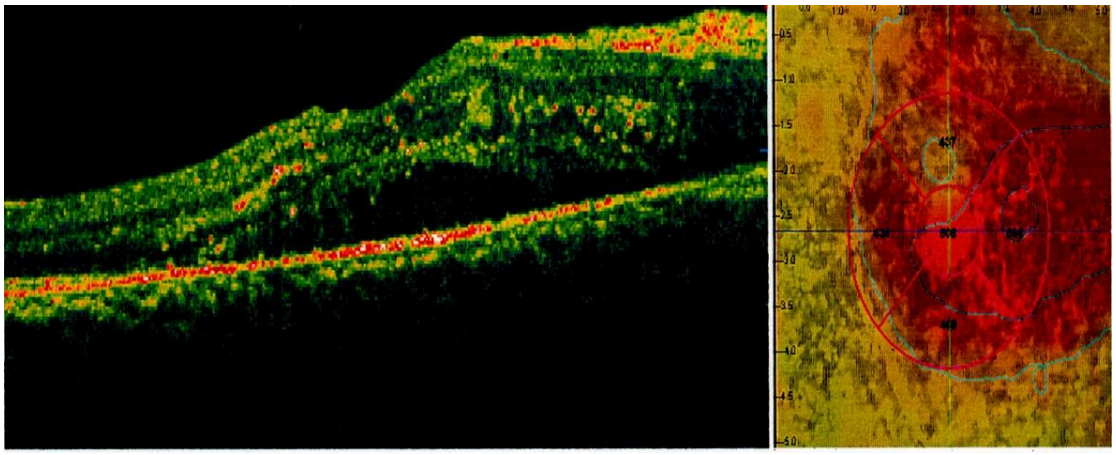


FIGURE 2: Post treatment showing 50% reduction in macular thickness.

CASE – 5

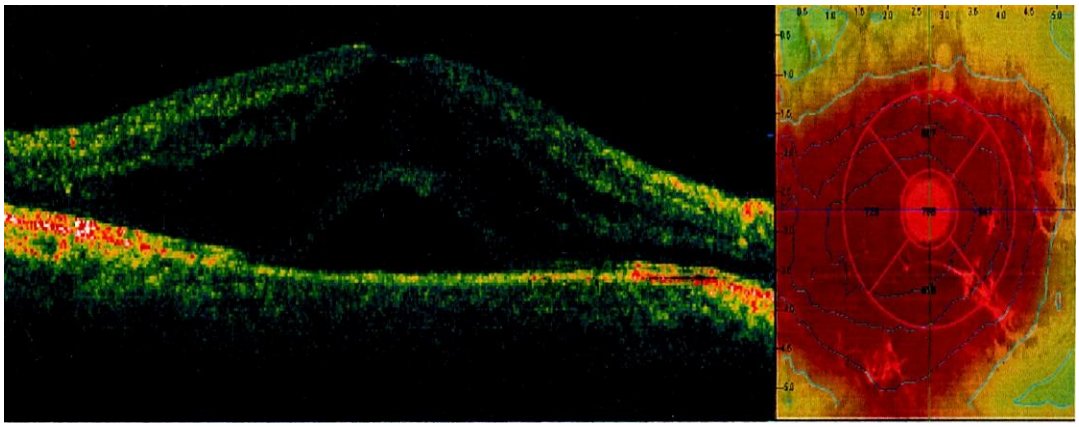


FIGURE 1: Pre treatment

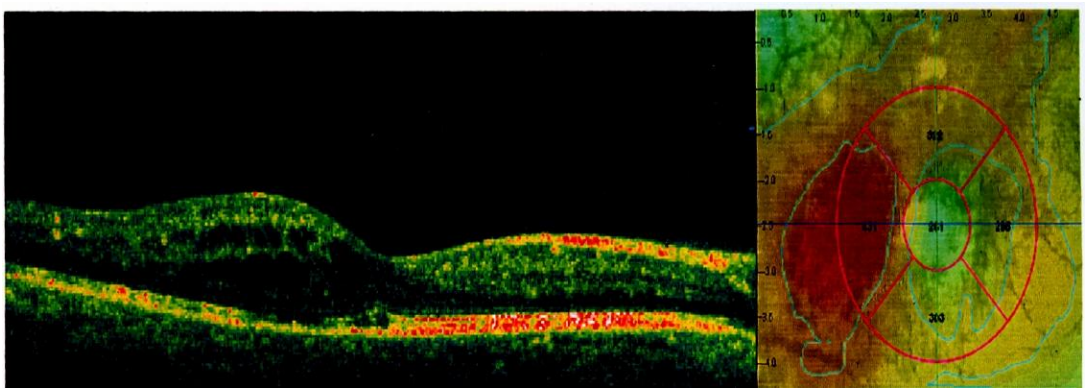


FIGURE 2: Post treatment reduction in macular edema

PART - III

REFERENCES

1. Green WR. RETINA. In: Spencer WH, ed. Ophthalmic Pathology: An Atlas and Textbook. 4th ed. Vol.2. Philadelphia: WB Saunders; 19996:673.

2. Green WR, Sebag J. Vitreoretinal interface. In: Ryan SJ, Ogden TE, Hinton DR, et al, eds. Retina. 3rd ed. Vol. 3. St. Louis: Mosby; 2001:1886-91.

3. Duke-Elder S. System of Opthalmology, vol 10- Diseases of the Retina, St Louis, C.V Mosby Company, 1967.

4. Ryan SJ, Retina , Vol 1, 2 , CV Mosby Company, 2004.

5. Johnson MW, Etiology and Treatment of macular edema, Am J Ophthalmo 20009;147:11-21.

6. Wright PL Wilkinson CP, Balyeat HD, Popham J, Reinke M Angiographic cystoid macular edema after posterior chamber lens implantation. Arch Ophthalmol 1988;106:740-744.

7. Photocoagulation for diabetic macular edema. Early treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study Research group. Arch Ophthalmology 1985;103(12): 1796-806.

8. Argon laser photocoagulation for macular edema in branch vein occlusion. Tthe Branch Vein Occlusion Study Group. Am J Opthalmol 1984;98(3):271-278.

9. Van Kooji B, De Boer J, Ten Dam N, et al. The effect of non-steroidal anti-inflammatory on inflammatory cystoid macular edema . Am J Ophthalmol 2005:140(3):563-4.

10. Flach AJ, Jampol LM, Weinberg D, et al. Improvement in visual acuity in chronic aphakia and pseudophakic cystoid macular edema after treatment with topical 0.5% ketorolac tromethamine. Am J Ophthalmol 1991;112(5):514-9.

11. Kapin MA, Yanni JM, Brady MT, et al. Inflammaion – mediated retinal edema the rabbit is inhibited by topical nepafenac. Inflammation 2003;27(5):281-91.

12. Kapin MA, Yanni JM, Brady MT, et al. Inflammaion – mediated retinal edema the rabbit is inhibited by topical nepafenac. Inflammation 2003;27(5):281-91.

13. Whitcup SM, Csaky KG, Podgor MJ , et al. A randomized , masked, cross-over trial of acetazolamide for cystoid macular edema in patients with uveitis. Ophthalmology 1996;103(7):1054-62; discussion 62.

14. Farber MD, Lam S, Tessler HH, et al. Reduction of macular edema by acetazolamide in patients with chronic iridocyclitis : a

randomized prospective cross over study. Br J Opthalmol 1994;78(1):4-7 .

15. Sze PY, Iqbal Z. Glucocorticoid actions on synaptic plasma membranes: Modulation of 1125 calmodulin binding. J Steroid Biochem Mol Biol 1994;48:179-86.

16. Gregorii NZ, Rosenfeld PJ, Puliafito Ca , et al. One- year safety and efficacy of intravitreal triamcinolone acetonide for the management of macular edema secondary to central retinl ven occlusion. Retina 2006;26(8):889-95.

17. Androudi S, Letko E, Meniconi M, et al. Safety and efficacy of intravitreal triamcinolone acetonide for uveitic macular edema. Ocul Immunol inflamm 2005;13(2-3):205-12.

18. Cunningham ET, Jr., Adamis AP, Altaweel M, et al. A phase II randomized double-masked trial of pegatinib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology 2005;112(10):1747-57.

19. Nguyen QD, Tatlipinar S, Shah SM, et al. Vascular endothelial growth factor is a critical stimulus for diabetic macular edema. Am J Ophthlmol 2006;142:961-9.

20. Haritoglou C, Kook D, Neubauer A, et al. Intravitreal bevacizumab (Avastin) therpy for persistent diffuse diabetic macular edema. Retina 2006;26(9):999-1005.

21. Daniel M.Taylor et al. Survey Ophthalmol 2006; 25(7):112-6

22. Marvin L.Sears, Surv.Ophthalmol 28 (suppl) : 525-534,1984

23. Jaffe,s cataract surgery 3rd edition.

24. Schepens CL et al (Ophthalmology 96 (10) : 1511-6,1989,Oct)

25. Martidis A, Duker J.S, Greenberg PB, et al. Intravitreal Triamcinolone for refractory diabetic macular edema. Ophthalmology 109:920-7,2002.

26. Karacorlu M, Ozdemir H, Intravitreal Triamcinolone Acetonide for treatment of chronic pseudophakic cystoid macular edema,Acta ophthalmol Scand, 2003 Dec, 81(6):648-52.

27. Audren H, Massin P, Haouchine B et al: Intravitreal triamcinolone for diabetic diffuse macular edema : preliminary results of discussion prospective controlled trial Ophthalmology 111 218-24, Discussion 224-5,2004.

28. Gilles MC,Kuzniarz M, Craig J et al : Intravitreal triamcinolone induced elevated intraocular pressure is associated with development of posterior subcapsular cataract, Ophthalmology 112;139-43,2005.

29. Boscia F, Furino C, Dammaco R, Ferreri P, S Borgia L, S Borgia C : Intravitreal triamcinolone acetonide in refractory pseudophakic

cystoid macular edema : functional and anatomic results, Eur J Ophthalmol 2005 Jan – Feb 15(1) :89-95.

30. Rhee DJ , Peck RE, Belmont J, et al. : Intraocular pressure alterations following intravitreal triamcinolone, Br J Ophthalmol 90 : 999 – 1003, 2006.

31. The SCORE study Clinical studies Database , NEI, http://www.nei.nih.gov/neitrials/view studyweb.aspx?id=99, Accessed 7/9/2007.

PROFORMA FOR CLINICAL STUDY ON CYSTOID MACULAR EDEMA

1. NAME :
2. AGE/SEX :
3. OP/IP No. :
4. OCCUPATION :
5. ADDRESS :
6. PHONE No. :
7. PRESENTING COMPLAINTS-

A) DEFECTIVE VISION- RE/LE
MILD/MOD/SEVERE/GRADUAL/SUDDEN
DURATION

B) OTHER COMPLAINTS- PAIN/REDNESS/ WATERING/ PHOTOPHOBIA/METAMORPHOSIA/POSITIVE SCOTOMA

C) DETAILS OF ANY SURGERY- TYPE OF SURGERY ANY COMPLICATION DURING SURGERY- PC RENT, VITREOUS DISTURBANCE,
DATE OF SURGERY
POST OPERATIVE COMPLICATION- SK, IRITIS, IRIS PROLAPSE, IOL POSITION, PUPILLARY CAPTURE, PCO
TYPE AND DURATION OF TOPICAL MEDICATIONS

D) HISTORY OF SYSTEMIC CONDITIONS- DM, HT, IHD, RENAL DISEASE

E) HISTORY OF DM- IDDM/NIDDM
DURATION
STAGE OF DIABETIC RETINOPATHY
TREATMENT DETAILS(OHA/INSULIN)
OCULAR TREATMENT(PRP/GRID)-
No. Of sittings
OTHER SYSTEM INVOLVEMENT-

NEPHROPATHY/NEUROPATHY
UNDER CONTROL/NOT

F) HISTORY OF HYERTENSION- DURATION
UNDER CONTROL WITH DRUGS
ANY ASSOCIATED IHD, HYPERLIPIDEMIA, CVA

8. EXAMINATION-
1] UCVA/BCVA/VA WITH PH
RE LE
2] ANTERIOR SEGMENT- SLE
3] IDO AND 90D-
4] IOP
5] COLOUR VISION
6] FIELDS

9. INVESTIGATION- 1] FBS/PPBS
2]URINE ALB/SUGAR
3]SERUM CHOLESTEROL(IN RVO)
5]BP

10. FUNDUS PHOTO
11. FFA-
12. OCT- MACULAR THICKNESS
DIAGNOSIS -
13. IVTA-Y/N
DATE
NO/OF SITTINGS
PRE V/A
FOLLOW UP- NEXT DAY- VA /IOP/FUNDUS/
ANT SEGMENT
1 WEEK
4WEEKS
8WEEKS
12 WEEKS
RPT OCT- CMT
RPT INJECTION NEEDED-Y/N

INDEX TO MASTER CHART

SEX	-	M – Male
		F – Female
DM	-	Diabetes mellitus
		Y – Yes
		N – No
		1 – No Diabetic retinopathy
		2 – Mild NPDR
		3 – Moderate NPDR
		4 – Severe NPDR
		5 – Very severe NPDR
		6 – PDR
HT	-	Hypertension
EYE AFFECTED	-	RE – Right eye
		LE – Left eye
DIAGNOSIS	-	1 – Pseudophakic CME
		2 – Retinal vein occlusion with CME
		3 – Diabetic CME
VA	–	Visual acuity
PH	–	Pin hole
NIP	–	Not improving with pinhole
PVD	–	Posterior vitreous detachment
		1 – No PVD
		2 – Incomplete PVD
		3 – Complete PVD
IOP	–	Intraocular pressure (in mmHg)
OCT	–	Optical coherence tomography
CMT	–	Central macular thickness (in µm)

MASTER CHART

S.No.	NAME	AGE	SEX	DM	HT	PVD	EYE AFFECTED	DIAGNOSIS	VA ON PRESENTATION	VA 4WEEKS	VA 8WEEKS	VA 12 WEEKS	PRE CMT	CMT 8WEEKS	CMT 12WEEKS	INITIAL IOP	IOP 1WEEK	IOP 12 WEEKS	COMPLI
1	KANAGASABAI	56	M	N	N	3	LE	1	4/60 NIP	4/60PH6/60	6/60PH6/36	6/24NIP	918	636	358	14	14	14	-
2	MOHAMMED SAQUEB	52	M	Y3	Y	1	LE	3	6/60PH6/36	6/60PH6/36	6/36PH6/24	6/36PH6/24	754	476	325	16	16	16	ERM
3	KUPPAMMAL	52	F	Y3	N	1	LE	3	6/36NIP	6/36PH6/24	6/24PH6/18	6/12PH6/9	370	285	190	16	16	16	-
4	MURUGAVEL	54	M	N	Y	3	RE	2	6/36PH6/24	6/24PH6/18	6/18PH6/12	6/18PH6/12	354	276	185	18	18	16	-
5	RAJA	47	M	Y6	N	1	RE	3	6/60PH6/36	6/60PH6/36	6/36PH6/24	6/24PH6/18	836	498	298	16	16	16	-
6	MARIMUTHU	66	M	Y1	N	1	RE	1	6/36PH6/24	6/36PH6/24	6/24PH6/12	6/12NIP	550	350	229	12	12	14	ERM
7	ASOKAN	49	M	Y3	N	1	LE	3	6/24NIP	6/24PH6/18	6/18PH6/12	6/12PH6/9	350	212	194	14	22	14	-
8	DEVARAJULU	68	M	Y4	Y	2	LE	3	4/60 NIP	2/60 NIP	2/60 NIP	2/60 NIP	471	312	205	18	24	18	-
9	KANNAYIRAM	73	M	N	N	2	RE	1	4/60PH6/60	5/60PH6/60	6/60PH6/36	6/36 NIP	974	534	312	18	18	18	-
10	SELVANAYAGAM	68	M	Y4	N	1	RE	3	6/60 NIP	6/36PH6/24	6/18PH6/12	6/12NIP	589	312	185	12	12	12	-
11	ANNAPOORANI	58	F	N	N	1	RE	1	6/60 NIP	6/60PH6/36	6/24PH6/18	6/18PH6/12	563	338	224	18	18	18	-
12	DAKSHINAMOORTHY	60	M	Y6	N	1	LE	3	3/60PH6/60	5/60PH6/60	6/36PH6/24	6/24PH6/18	1153	445	290	18	18	18	-
13	SAROJA	58	F	Y4	Y	1	RE	3	6/60NIP	6/60PH6/36	6/36PH6/24	6/18NIP	476	320	198	14	14	14	-
14	JAGANATHAN	65	M	Y3	N	1	RE	1	6/60PH6/24	6/36PH6/24	6/18PH6/12	6/12PH6/9	860	454	254	18	18	18	-
15	ELUMALAI	42	M	Y5	N	3	RE	3	6/60PH6/36	6/36PH6/18	6/24PH6/12	6/24PH6/12	897	512	240	14	14	14	-
16	RAJENDRAN	62	M	N	Y	3	RE	2	4/60 NIP	4/60NIP	4/60PH6/60	6/60PH6/36	745	510	240	20	20	20	ERM
17	GANGADHARAN	59	M	Y4	N	2	RE	3	5/60NIP	6/60NIP	6/60NIP	6/60NIP	618	376	220	18	22	24	ERM
18	SUNDARAMMAL	66	F	Y4	N	1	RE	3	6/60NIP	6/60PH6/36	6/24PH6/18	6/18NIP	600	474	320	16	16	16	-
19	KASTHURI	40	F	N	N	2	LE	1	6/24NIP	6/24NIP	6/24PH6/18	6/18PH6/12	754	554	336	18	16	16	LAMELLAR HOLE
20	BABU	33	M	Y4	Y	2	LE	3	6/60PH6/36	6/36PH6/24	6/24NIP	6/24NIP	836	536	398	14	14	14	ERM
21	KANNIYAPPAN	72	M	Y3	N	1	LE	1	5/60PH6/36	6/60PH6/24	6/24PH6/18	6/18 NIP	608	373	229	14	14	14	-
22	VIJAYARAGHAVAN	7	M	Y6	N	3	RE	3	6/36PH6/18P	6/36PH6/24	6/24PH6/18	6/12PH6/9	633	334	279	18	18	18	-
23	BABYAMMAL	61	F	N	Y	2	LE	2	2/60PH3/60	4/60PH6/60	4/60PH6/60	6/60PH6/36	494	280	197	16	18	16	ERM
24	ELUMALAI	42	M	Y5	N	1	LE	3	6/36PH6/24	6/24PH6/18	6/18PH6/12	6/18PH6/12	750	390	220	16	16	16	-
25	REVATHI	65	F	Y5	N	1	LE	3	6/36NIP	6/24PH6/18	6/18PH6/12	6/12NIP	598	378	224	14	14	14	-
26	ASOKAN	70	M	N	Y	3	RE	1	4/60PH6/60	6/60PH6/36	6/36PH6/24	6/24NIP	794	458	302	18	28	18	-
27	AHMED	62	M	Y4	N	1	LE	3	2/60NIP	2/60 NIP	4/60NIP	4/60 NIP	758	498	216	18	22	18	-
28	GOVINDARAJ	50	M	Y3	Y	1	RE	2	6/60PH6/36	6/36PH6/24	6/24PH6/18	6/18PH6/12	389	264	202	16	16	16	-
29	MEENA	60	F	Y4	N	1	RE	3	6/60PH6/24	6/60PH6/24	6/24PH6/12	6/12PH6/9	393	210	185	16	16	16	-
30	REVATHI	65	F	Y5	N	3	RE	3	6/36PH6/24	6/24PH6/18	6/18PH6/12	6/12 NIP	538	354	210	14	14	14	-
31	KOTHANDAN	63	M	N	Y	2	LE	1	2/60PH5/60	3/60PH5/60	5/60 NIP	5/60NIP	903	754	645	14	14	14	-
32	MALARVIZHI	59	F	Y5	Y	3	LE	3	3/60PH6/60	5/60PH6/60	6/36NIP	6/36NIP	842	365	195	20	22	18	-
33	ASOKAN	70	M	N	Y	1	LE	1	6/60PH6/36	6/36PH6/24	6/24PH6/18	6/18NIP	663	393	250	18	24	18	-
34	DAKSHINAMOORTHY	60	M	Y4	N	1	RE	3	6/60PH6/36	6/36PH6/24	6/24PH6/18	6/18NIP	1049	460	312	16	18	16	-
35	MALLIGA	56	F	Y3	N	3	RE	3	6/36NIP	6/36PH6/24	6/24PH6/18	6/18PH6/12	462	312	208	16	16	16	-
36	SELVARANI	52	F	Y1	Y	1	LE	2	5/60PH6/60	6/60PH6/36	6/36PH6/24	6/24NIP	724	578	290	14	14	14	-
37	BABU	33	M	Y4	Y	2	RE	3	6/36PH6/24	6/36PH6/24	6/24NIP	6/24NIP	479	458	312	14	14	14	ERM
38	KOTHANDAN	63	M	N	Y	2	RE	1	5/60PH6/60	6/60PH6/36	6/36 NIP	6/36 NIP	807	504	299	14	12	12	-
39	MALARVIZHI	59	F	Y6	Y	1	RE	3	3/60PH6/60	5/60PH6/60	6/60NIP	6/60NIP	947	422	212	20	26	18	-
40	SUNDARAMMAL	66	F	Y4	N	1	LE	3	6/60NIP	6/36PH6/24	6/24PH6/18	6/12NIP	690	412	298	16	16	16	-